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16. ABSTRACT

Phosgene is primarily manufactured for the synthesis of isocyanate-based polymers, carbonic acid esters, and acid chlorides. Annual production volume in the U.S. is estimated to be above one billion pounds. Ambient and indoor air concentrations of phosgene are produced by direct emissions during its manufacture, handling, and use; thermal decomposition of chlorinated hydrocarbons; and photochemical oxidation of chloroethylenes in the air. In the atmosphere, the most important sinks for the removal of phosgene are heterogeneous decomposition and slow liquid-phase hydrolysis. Phosgene, an acutely toxic gas, was once used in chemical warfare. The effects of acute inhalation exposure are primarily respiratory, causing pulmonary emphysema, pulmonary edema, and possibly death due to paralysis of the respiratory center as a result of anoxia. Persistent effects of acute phosgene poisoning may involve organs other than the lungs, primcipally the brain, though these effects are thought to be the result of anoxia caused by pulmonary edema. Limited epidemiology studies indicate no increase in the incidence of cancers among workers chronically exposed to phosgene. No definitive conclusions can be drawn regarding possible teratogenic, reproductive, carcinogenic, or mutagenic effects of phosgene exposure because adequate studies have not been performed.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
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PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for EPA use. The health assessment was originally developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of phosgene as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

The relevant literature for this document has been reviewed through January 1986. In addition, selected studies of more recent publications (July 1986) have been incorporated in the sections on phosgene toxicology.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, a considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

ABSTRACT

Phosgene ($COCl_2$) is primarily manufactured for the synthesis of isocyanate-based polymers, carbonic acid esters, and acid chlorides. Annual production volume in the United States is estimated to be above one billion pounds. Ambient and indoor air concentrations of phosgene are produced by (1) direct emissions during its manufacture, handling, and use; (2) thermal decomposition of chlorinated hydrocarbons; and (3) photochemical oxidation of chloroethylenes in the air. In the atmosphere, the most important sinks for the removal of phosgene are heterogeneous decomposition and slow liquid-phase hydrolysis.

Phosgene, an acutely toxic gas, was once used in chemical warfare. The effects of acute inhalation exposure are primarily respiratory, causing pulmonary emphysema, pulmonary edema, and possibly death due to paralysis of the respiratory center as a result of anoxia. Persistent effects of acute phosgene poisoning may involve organs other than the lungs, principally the brain, though these effects are thought to be the result of anoxia caused by pulmonary edema.

Limited epidemiology studies indicate no increase in the incidence of cancers among workers chronically exposed to phosgene. No definitive conclusions can be drawn regarding possible teratogenic, reproductive, carcinogenic, or mutagenic effects of phosgene exposure because adequate studies have not been performed.

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1. SUMMARY AND CONCLUSIONS

1.1 BACKGROUND INFORMATION

Phosgene ($COCl_2$) is a colorless, highly toxic gas at ambient temperature and pressure. At low concentrations, phosgene has been described as having a characteristic odor similar to that of moldy hay; at higher concentrations it has an irritating, pungent smell. Phosgene gas is only slightly soluble in water, and rapidly decomposes in solution to yield carbon dioxide and hydrochloric acid. Synonyms for phosgene include carbonyl chloride, carbonic dichloride, carbon oxychloride, and chloroformyl chloride.

John Davy first synthesized phosgene in 1812 by the photochemical reaction of carbon monoxide and chlorine, using activated charcoal as a catalyst. The name phosgene was given to the gas to indicate the role played by sunlight in its formation. Originally, the main uses of phosgene were in the manufacture of aniline dyes and certain pharmaceutical preparations such as creosotal, hedonal, and aristochin. However, it was not used in major quantities until 1915, when Germany began using it as a chemical warfare agent. Production dropped off after World War I, but was sharply increased in the early 1940's in anticipation of a resurgence of chemical warfare in World War II. Industrial uses for phosgene began in about 1955, when it was used as an intermediate in the manufacture of toluene diisocyanate. The U.S. International Trade Commission (USITC) reported that the volume of phosgene produced in 1957 was five million pounds. Phosgene production increased rapidly through the 1970's as the demand for diisocyanates increased and other uses for phosgene were found.

Presently, phosgene is produced in a manner very similar to that used by Davy in 1812; equimolar amounts of anhydrous chlorine gas and high-purity carbon monoxide are reacted in the presence of a carbon catalyst. Production volumes, as reported to the USITC, have been relatively constant through the 1980's, generally staying slightly above one billion pounds per year. However, these reported volumes may be lower than actual production volumes because a large amount of the phosgene produced is used captively in the formation of other end products and therefore not reported to the USITC. Current industrial uses for phosgene include the synthesis of isocyanate-based polymers, carbonic acid esters, and acid chlorides. It is also used in the production of dye intermediates and pesticides and in metallurgy for separating ores.

Workplace exposures to phosgene do not arise solely from the manufacture, handling, and use of phosgene. Potentially lethal levels of phosgene can be generated by the decomposition of chlorinated hydrocarbons. Solvents that have been shown to decompose when in contact with an open flame or a hot metal surface to form phosgene include methylene chloride, chloroform, carbon tetrachloride, Freon, trichloroethylene, and perchloroethylene. Therefore, workers involved in the use of these solvents near a heat source (e.g., welders, firemen, painters) as well as phosgene workers are potentially at risk. In 1976, the National Institute for Occupational Safety and Health (NIOSH) estimated that 10,000 workers were potentially exposed to phosgene in the workplace. However, preliminary data from the National Occupational Exposure Survey, conducted by NIOSH from 1980 to 1983, indicated that 2358 workers were potentially exposed to phosgene in the workplace in 1980. The current Threshold Limit Value - Time Weighted Average (TLV - TWA) for phosgene; the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed daily without adverse effect, as determined by the American Conference of Governmental Industrial Hygienists, is 0.1 ppm (0.4 mg/m^3).

Direct atmospheric emissions of phosgene, as well as the thermal decomposition of chlorinated hydrocarbons, are generally contained; although they may pose a significant indoor hazard in industrial and residential settings, they constitute only a negligible contribution to phosgene levels in the environment. Of far greater consequence is the photochemical oxidation of the chloroethylenes. The two major chloroethylenes that contribute to the atmospheric pool of phosgene are perchloroethylene and trichloroethylene. Phosgene levels have been measured in ambient air using a gas chromatograph equipped with two electron capture detectors. In rural areas of California, phosgene was present at an average concentration of 21.7 parts per trillion (ppt), while in California's urban areas the average was 31.8 ppt. The highest level recorded was measured over Los Angeles, 61.1 ppt, although it has been suggested that higher levels may be reached under highly stagnant weather conditions.

Investigations into the atmospheric fate of phosgene have shown that at least two tropospheric sinks exist for its elimination. One sink is heterogeneous decomposition; phosgene will decompose when in contact with most surfaces, especially at elevated temperatures. The second sink is liquid-phase hydrolysis. In one case, an intermittent rainfall that lasted from 50 to 60 hours reduced the ambient air concentrations of phosgene by 15 to 20 percent. Other studies indicated that tropospheric loss of phosgene through photolysis, gas-phase hydrolysis, or gas-phase reactions involving O· and OH· radicals is insignificant. Because of the existence of at least two major tropospheric sinks, it is unlikely that phosgene will have an adverse impact on the stratosphere.

1.2 PHOSGENE METABOLISM

The low solubility of phosgene in water enhances its acute toxicity by allowing the inhaled gas to penetrate into the alveolar spaces. The amount of the gas that does go into solution is rapidly hydrolyzed to form carbon dioxide and hydrochloric acid. The amount of hydrochloric acid produced after inhalation of lethal doses of phosgene is believed to be toxicologically insignificant. However, the reaction of phosgene with water is much slower than its reaction with other chemical groups such as $-NH_2$, -OH, or -SH groups. The metabolism of phosgene in laboratory animals has not been studied. However, *in vitro* studies and chemical measurements on the reactivity of phosgene with proteins and various chemicals indicate that the pathology of phosgene toxicity is a result of its ability to directly acylate tissue components.

1.3 PHOSGENE TOXICOLOGY

Before World War I, essentially nothing was known of the health effects of phosgene. During the war, artillery shells were filled with liquid phosgene and fired amid enemy troops. Upon impact, the shells would explode, filling the air with phosgene gas. Frequently, troops dispensing the chemical would also be exposed as a result of leaky shells or because enemy artillery fire hit the stockpile of phosgene-filled shells. This resulted in thousands of men suffering from acute inhalation exposure to phosgene, with medical personnel having no idea how to treat them. It has been estimated that 80 percent of all gas deaths during World War I were due to phosgene exposure.

Soon after phosgene's deployment, American, French, Italian, British, and German scientists began animal studies to investigate its toxicity. Dosing was carried out to mimic the battlefield situations; concentrations were high enough to cause frank lesions, or death, and the route of exposure was invariably by inhalation. It was reported that, initially, phosgene appeared to specifically attack the terminal bronchioles of the lung. Other immediate effects, such as lacrimation, and irritation of the upper airways, were noted, but were relatively mild when compared to those caused by other warfare gases. The phenomenon of the "clinical latent phase," a period essentially devoid of serious symptomatology, was also noted. The duration of the clinical latent phase was found to be inversely proportional to the extent of exposure.

Several hours after the animals were exposed to phosgene, pulmonary edema became evident, sometimes increasing lung weights by as much as fourfold. At the height of the pulmonary edema, the blood of the animals assumed a sticky, concentrated consistency, leading to an enlargement of the right side of the heart. It was believed that phosgene exerted its toxic effect directly on the lung and that involvement of other tissues was a secondary effect. However, there was debate over the cause of death. Some scientists believed that death was due to pulmonary edema, while others believed it was a result of the hematological effects.

During this period, acute inhalation studies were performed on mice, rats, guinea pigs, rabbits, cats, dogs, goats, and monkeys. The pathological findings among species were essentially alike and agreed with the lesions seen in the victims exposed to the gas during the war. However, the susceptibility to the lethal effects of phosgene did vary among species. Cats were most susceptible, with an $L(CT)_{50}$ of ~200 ppm-min, followed by monkeys (~300 ppm-min), rats (~400 ppm-min), guinea pigs (~500 ppm-min), humans (~500 ppm-min), mice (~500 ppm-min), dogs (~1000 ppm-min), rabbits (~1500 ppm-min), and goats (~2000 ppm-min).

The concept of a "death product" was introduced by Fritz Haber to explain the relationship between the extent of exposure to phosgene and death. According to "Haber's Law," the biological effect of phosgene is directly proportional to the exposure expressed as the product of the atmospheric concentration (C) and the time of exposure (T); $CT = K$, where K can be death, pulmonary edema, or other biological effects of phosgene exposure. Haber's Law has been shown to be valid within certain limits by subsequent investigations. For man, phosgene exposures above 30 ppm-min can produce pulmonary damage, whereas an exposure of at least 150 ppm-min is necessary to produce clinical evidence of pulmonary edema (Table 1-1). The human $L(CT)_1$, $L(CT)_{50}$, and $L(CT)_{100}$ values, as shown in Table 1-1, have been estimated to be 300, 500, and 1300 ppm-min, respectively. It should be noted that in general, the reported exposure is the dose (CT) offered, not necessarily the biologically effective dose which is inhaled. For example, by holding the breath or keeping respiration shallow with reduced breath volume per minute, the inhaled dose may be much smaller than the dose that is offered.

TABLE 1-1. CONCENTRATION-EFFECT RELATIONSHIPS OF PHOSGENE EXPOSURE IN HUMANS

Perception of odor	>0.4 ppm
Recognition of odor	>1.5 ppm
Signs of irritation in eyes, nose, throat, and bronchi	>3 ppm
Beginning lung damage	>30 ppm-min
Clinical pulmonary edema	>150 ppm-min
$L(CT)_1$	~300ppm-min
$L(CT)_{50}$	~500 ppm-min
$L(CT)_{100}$	~1300 ppm-min

Post-World War I research elucidated many of the pathological lesions caused by phosgene inhalation, but very little was learned of its mechanism of action. In fact, it was not until the World War II era that researchers had enough evidence to show that phosgene binds directly to tissue macromolecules. Until that time, it was believed that phosgene was inhaled into the alveolar spaces where it slowly reacted with water to produce hydrochloric acid. Supposedly, it was the hydrochloric acid that produced the toxic lesions.

Although the exact mechanism of phosgene toxicity has still not been fully elucidated, many aspects are currently understood. When inhaled in concentrations sufficient to produce pulmonary edema, the course of phosgene poisoning proceeds through a series of phases that are common to all mammalian species investigated. Initially, phosgene interacts with sensory receptors within the bronchial tree to produce a bioprotective vagal reflex syndrome. This syndrome is characterized by the onset of rapid, shallow breathing, leading to reductions in vital capacity and respiratory volume. Subsequently, there is a drop in arterial oxygen partial pressure and blood pH, while arterial carbon dioxide partial pressure tends to increase. Cardiac symptoms are bradycardia and, occasionally, sinus arrhythmia. Other cholinergic symptoms such as increased salivation, nausea, urination, and defecation have been observed in animals. The intensity of the vagal reflex syndrome is not dose related, especially in humans where mental and emotional influences are important. The reflex shows a tendency to regress within hours after the exposure has ended.

Other immediate symptoms of phosgene exposure to concentrations above 3 ppm include irritation of the eyes and upper airways possibly due to the formation of hydrochloric acid. At higher concentrations (>200 ppm), phosgene produces apnea of several seconds' duration, bronchoconstriction, bronchial epithelium desquamation, and inflammatory bronchiolar changes.

After entering the lung, studies indicate that phosgene acylates tissue macromolecules in cells of the lowest extremity of the respiratory tract. The initial site of injury is still a point of debate, alveoli or bronchioles, and may depend on the dose. Nonetheless, animal necropsy observations have indicated damage to the bronchioles involving vacuoles in ciliated cells and Clara cells, extracellular septal edema, intracellular edema of the walls of the respiratory bronchioles, spastically constricted bronchioles, and emphysematous expansion of the distal segments. Alveolar damage has been shown to include edematous swelling and plicated surfaces of alveolar cells, lamellar inclusions in type II septal cells, disaggregated basal membranes, and decreased numbers of mitochondria in endothelial cells. Later anatomical defects include membrane rupture of single endothelial cells at the blood-air barrier.

In addition to the structural damage, numerous enzymes are inhibited by phosgene, and anoxia and cellular decay lead to the release of histamine and various enzymes. It has been suggested that enzyme inhibition and consequent disruption of pulmonary energy metabolism may play a major role in damage to lung tissue after exposure to phosgene.

The structural damage to the lung allows blood plasma to enter the interstices and alveoli. Depending on the dose, alveolar edema may become apparent after only a few minutes. The hematocrit value first shows a slight decrease, followed by a relatively late rise. Lymph drainage from the lung increases substantially. In animal studies, gas exchange across the blood-air barrier is inhibited relatively early; the impairment in diffusion has not yet been observed in humans. Arterial oxygen partial pressure tends to normalize, but then decreases towards the end of the clinical latent phase. The increasing acidosis is first of a respiratory type and then of a mixed respiratory and metabolic type.

Pulmonary edema increases until it becomes clinically evident. Gas exchange becomes insufficient, and the mucous membrane of the bronchi becomes necrotic and is shed. Leukocytes migrate into the bronchiolar walls and into the alveolar interstices. Pulmonary arterial pressure remains normal up to shortly before death. Death is usually due to paralysis of the respiratory center as a result of anoxia. However, if anoxia is treated effectively, thus prolonging life, death may still ensue due to circulatory shock or infection.

Although the mechanism of toxicity described above for phosgene inhalation is based mainly on animal data, it appears to hold for humans as well. After acute exposure to phosgene, patients usually experience mild to severe irritation of the eyes and throat; a dry, unproductive cough; nausea and vomiting; and occasionally a weak and dazed feeling. These initial symptoms are usually short-lived, lasting about 2 to 20 minutes, and are followed by a period of subjective well-being that can last from 1 to 24 hours, depending on the exposure. A few patients return to work during the clinical latent phase.

The end of the latent phase is usually marked by the onset of a cough accompanied by expectoration of frothy edema fluid. There is commonly a sensation of tightness or pain across the chest followed by shortness of breath and a choking sensation. The patient is usually restless, anxious, or agitated, and sometimes cyanotic. Clinical findings include hemoconcentration, leukocytosis, low systemic arterial pressure, and bilateral rales. The patient usually recovers completely, with typical hospital stays ranging from a few days to a couple of weeks.

Most victims of severe acute phosgene poisoning complain of symptoms for some time such as rapid, shallow breathing, shortness of breath on exertion, and general feelings of lassitude and reduced physical fitness. In general, though, physical examinations and chest roentgenograms typically indicate no physical damage; more sophisticated pulmonary function studies reveal abnormalities associated with emphysema. Pulmonary emphysema can also occur after multiple exposures to toxic levels of phosgene. The measurable changes in pulmonary function that are consistently observed vary in type and severity, but cannot be correlated with the severity of phosgene intoxication or with the chronic symptomatology. In most cases, these symptoms are not disabling and last from several months to several years, until they completely disappear. In patients where phosgene poisoning has led to chronic disability, the effects are more closely related to smoking habits, psychological disorders, or preexisting pulmonary abnormalities than to the severity of exposure. Persistent effects of acute phosgene poisoning have also involved organs other than the lungs, most notably the brain. Symptoms include neurasthenia, speech incoordination, paralysis, and Raynaud-like effects. These latter abnormalities are considered to be secondary effects of anoxia caused by pulmonary edema, or due to preexisting psychological disorders.

Questions exist as to whether repeated short-term or more chronic, continuous low-level exposures to phosgene might be associated with pulmonary or other effects analogous to those described above as being induced by acute high-level exposures. Based on the existing scientific literature, however, no definite conclusions can be drawn regarding pulmonary function effects associated with chronic exposure levels several orders of magnitude below those at which acute phosgene exposure effects are known to occur. Researchers have concluded that no significant human health effects have been found at phosgene concentrations below 0.1 ppm. The measured ambient concentrations of phosgene are much lower, the maximum being 61 ppt. The relationship of product of concentration and exposure time (CT) for phosgene exposure cannot be used to draw conclusions regarding chronic, low-level phosgene exposure. In general, the CT relationship is valid only between 1 and 200 ppm. Data on acute effects from phosgene exposure cannot be extrapolated to extended chronic exposure; thus, no clear inferences about chronic exposure effects can be drawn from the data on acute effects. More studies are required in order to evaluate the effects resulting from possible fenceline exposures.

In addition to the lack of evidence of pulmonary function effects being associated with chronic exposures, epidemiology studies indicate that there has been no increase in the incidence of cancers among workers chronically exposed to phosgene as compared to the population in general. Except for acute phosgene poisoning, there also appears to be no significant increase in the number of deaths in phosgene-exposed workers due to asthma, tuberculosis, or pulmonary disease as compared to the general population. While these studies are negative, they do not provide an adequate basis, due to study limitations, to draw conclusions regarding the likelihood of phosgene having a carcinogenic or pulmonary disease potential.

No studies have been performed to investigate the teratogenicity or reproductive effects of phosgene. There are no adequate long-term animal cancer bioassays for phosgene, and as previously mentioned the available epidemiologic data are inadequate to assess the carcinogenic potential in humans.

While there is at present no evidence for phosgene's role as a carcinogen agent, such a hypothesis exists because of its ability to induce the formation of adducts with cellular macromolecules and because phosgene is a metabolite of compounds with known carcinogenic activity. Overall, the carcinogenic data are inadequate to assess the carcinogenic potential of phosgene for humans and, according to the Environmental Protection Agency's Carcinogen Risk Assessment Guidelines, phosgene is a group D compound.

1.4 RESEARCH NEEDS

Essentially the same research needs exist now as when the National Institute for Occupational Safety and Health (NIOSH) published its criteria document on phosgene in 1976. Chronic toxicity studies need to be performed in laboratory animals with inhalation exposures [illegible] phosgene at or near 0.1 ppm. These studies should also address the issues of carcinogenicity, mutagenicity, teratogenicity, and reproductive effects in both male and female animals. Furthermore, additional epidemiologic studies are needed to provide more information on the human health effects of long-term, low-level exposures to phosgene. Research is also needed on the reproductive and fetotoxic effects of high doses of phosgene in animals, and followup studies of humans who have been previously exposed to high levels of phosgene are needed to better understand the persistence of chronic symptomatology.

2. BACKGROUND INFORMATION

2.1 PHYSICAL AND CHEMICAL PROPERTIES OF PHOSGENE

Phosgene is also commonly referred to as carbonyl chloride, carbon oxychloride, carbonic dichloride, and chloroformyl chloride. It is a colorless, highly toxic gas under conditions of ambient temperature and pressure. Phosgene is produced by mixing pure chlorine gas with purified carbon monoxide in the presence of activated charcoal. When in contact with large amounts of air, phosgene has an odor reminiscent of moldy hay (Windholz, 1983). It is a planar molecule with interatomic distances of 0.128 and 0.168 nm between C-O and C-Cl, respectively. It is used in the synthesis of isocyanate-based polymers, polycarbonates, carbonic acid esters, acid chlorides, dye intermediates, and pesticides, and in metallurgy for the separation of ores (Beard, 1982). The physical and chemical properties of phosgene are presented in Table 2-1.

2.2 QUANTITATION AND ANALYSIS

Phosgene inhalation can result in death if prompt, appropriate medical attention is not provided. The proper medical treatment for an individual exposed to phosgene depends on the concentration and length of the exposure (Diller et al., 1979). It is, therefore, essential to have a means by which to monitor both exposure time and concentration levels whenever this gas is present in the work environment. A number of techniques are presently used to determine phosgene concentrations in air. These include passive dosimetry, manual colorimetry, automatic colorimetry, gas chromatography, infrared spectroscopy, and paper tape monitoring.

The passive dosimeter is a popular device with phosgene workers and medical personnel because it measures the concentration of phosgene gas present in the breathing zone of each worker (Moore and Matherne, 1981; Diller et al., 1979). This device consists of a small clip-on badge that contains a piece of paper tape that has been saturated with 4(4'-nitrobenzyl)pyridine. Phosgene

TABLE 2-1. PHYSICAL AND CHEMICAL PROPERTIES OF PHOSGENE

Parameter	Value	Reference
CAS number	75-44-5	Hardy (1982)
Molecular formula	$COCl_2$	Windholz (1983)
Molecular weight	98.92	Windholz (1983)
Conversion factor	1 ppm = 4.043 mg/m^3	
Solubility		
Water	Decomposes in water	Windholz (1983)
Organic solvents	Decomposes in alcohol; very soluble in benzene, toluene, glacial acetic acid, and most liquid hydrocarbons	Beard (1982)
Melting point	-104°C	Beard (1982)
	-101-127°C	Verschueren (1983)
	-118°C	Windholz (1983)
Boiling point	8.3°C	Beard (1982)
	8.2°C	Windholz (1983)
	8.1°C	Verschueren (1983)
Vapor pressure		
20°C	1215 mmHg	Windholz (1983)
	1.6 atm	Verschueren (1983)
30°C	2.2 atm	Verschueren (1983)
Vapor density	3.42	Verschueren (1983)
Density		
d_4^{19}	1.392	Verschueren (1983)
d_4^{0}	1.432	Windholz (1983)

reacts with the treated tape to produce a deep red color. The sensitivity and color stability of the dosimeter can be increased by the addition of an acid acceptor such as N-phenylbenzamine (Noweir and Pfitzer, 1971). The color intensity indicated by the tape is logarithmically proportional to the phosgene exposure, with a range of 2 to 100 ppm-min (Matherne et al., 1981). The advantages of this monitoring system over the others is that it measures personal exposures; the badge can be worn anywhere that is convenient for the individual, provided the tape is exposed to the air; and it provides immediate information on the exposure dose, which can be used to decide what, if any, medical treatment is needed. An extensive review on reagents that react colorimetrically with phosgene can be found in a report prepared by the Atlantic Research Corporation (Snyder et al., 1983).

Comparisons of the other five detection methods have been made (Tuggle et al., 1979; Kistner et al., 1978), and the results are presented in Table 2-2. The authors concluded that three of the techniques, automated colorimetry, gas chromatography, and infrared spectrophotometry, showed promise of attaining the sensitivity to detect levels of phosgene below its present threshold limit value (TLV, 0.1 ppm) and of being adaptable to real-time monitoring. Other reports (Enviro Control Inc., 1981) also indicate that the paper tape monitor is an excellent method for monitoring phosgene levels in the workplace. A brief description of each of these five methods is provided below (Tuggle et al., 1979).

In the manual colorimetric method, air is drawn through a midget impinger containing a diethylphthalate (DEP) solution of 4(4'-nitrobenzyl)pyridine (NBP) and N-benzylaniline (BA). The subsequent color change of the solution is measured in a spectrophotometer at a wavelength of 475 nm. A 25-minute air sample drawn at a rate of 1 L/minute into 10 mL of reagent is recommended for a detection range of 0.05 to 1.0 ppm of phosgene (American Industrial Hygiene Association, 1969). The method has the advantage of proven dependability through extended use, and was the recommended method at one time (National Institute for Occupational Safety and Health, 1976). However, its response time (see Table 2-2) is much too slow to be useful as a continuous monitoring device.

In automated colorimetry, sample air is bubbled into a flowing stream of NBP-BA-DEP reagent. While passing through the machine's mixing coils, any phosgene in the sample will react with the reagent, causing a color change. Air bubbles are separated from the liquid, which then flows to a colorimeter where its absorbance is measured. In this process, air is sampled at 1 L/minute, and the NBP-BA-DEP reagent flow rate is 0.2 mL/minute. The limit of detection for this method is 0.001 ppm of phosgene. A drawback of this method is its long response time, allowing phosgene leaks to go undetected for up to 20 minutes.

Of all the methods, gas chromatography equipped with an electron capture detector has proven to be the most sensitive for phosgene detection. Tuggle et

TABLE 2-2. COMPARISON OF FIVE METHODS FOR THE DETECTION, QUANTIFICATION, AND MONITORING OF PHOSGENE

Specification	NIOSH--recommended[a]	Manual colorimetry	Automated colorimetry	Gas chromatography	Infrared spectrophotometry	Tape monitor
Alarm	Set for 0.2 ppm	None	None, but adaptable	None	None, but adaptable	Yes
Response time	<90 sec for alarm	30 min (samp./anal.)	10-20 min	3-6 min	30 sec	5-15 sec
Drift	<1% fullscale in 24 hr	Drift corrected	1%/24 hr	>1%/24 hr	<1%/24 hr	<1%/24 hr
Noise	<1% fullscale		0.5%	1%	10% at 0.2 ppm Fullscale	0.25%
Accuracy	±10% of signal, 0.05-0.4 ppm	±20%	±15%	±15%	±10%	±15%
Precision	±5% fullscale	±15%	±6%	±10%	±4%	±6%
Specificity	If interferences, known responses	Specific	Specific	Specific	Trichloroethylene, response known	Specific
Operating range	0-0.4 ppm	0-0.4 ppm	0-0.4 ppm	0-0.4 ppm	0-0.4 ppm	0-0.4 ppm
Operation	168 hr continuous		24 hr continuous	8 hr continuous with auto sampling valve	168 hr continuous	168 hr continuous
Explosion hazard	Safe in explosion hazard areas	Yes, with G2-approved pump	Yes, with G2-approved pump	No	Yes, with G2-approved pump	Yes
Detection limit	<0.05 ppm	0.05 ppm	0.001 ppm,	0.0001 ppm	0.02 ppm	0.005 ppm
Operating limit		25 ppm	1 ppm	5 ppm	300 ppm	40 ppm
Calibration freq.		30 days	24 hr	8 hr	7 days	7 days
Operator attention		Every 30 min	Once daily	Manual op.: constant; automated: recommended	Once weekly--daily checks recommended	Once weekly--daily checks
Down time		None	Occasional	Occasional	Very infrequent	Very infrequent
Sample rate		1 L/min	1 L/min	0.5 mL injection	2-5 L/min	0.4 L/min
Operator expertise		Minimal	Moderate	Skilled	Minimal	Minimal
Portability		Depends on spectrophotometer	Portable--150 lb	Portable	Portable	Portable

[a] National Institute for Occupational Safety and Health (1976) Criteria Document on Phosgene.

Source: Adapted from Tuggle et al. (1979); Kistner et al. (1978).

al. (1979) list the limit of detection for this method at 0.0001 ppm (Table 2-2); however, several researchers have used this method to measure ambient air levels of phosgene in the parts per trillion (ppt) range (Singh et al., 1977). Another advantage that the gas chromatograph provides is its high specificity for phosgene. Disadvantages include the need for a trained technician to operate and maintain the system, occasional down time, and frequent column degradation due to the corrosiveness of phosgene. This latter problem has been diminished somewhat by the use of Teflon columns packed with Chromosil 310[c].

Infrared spectroscopy has been used to record phosgene levels as low as 0.025 ppm (Esposito et al., 1977). One infrared field machine uses a compact infrared analyzer in conjunction with a 20-m variable path length cell. Air is drawn into the machine, and the absorbance at a sample wavelength where phosgene absorbs (11.8 µm) is measured directly against the reference wavelength of 11.2 µm, which is a blank region for phosgene. The difference in absorbance corresponds to the phosgene content of the air (Tuggle et al., 1979).

Paper tape monitors have recently measured phosgene concentrations as low as 0.005 µg/L (Hardy, 1982). One commercially available detection system draws sample air through the top half of a chemically treated tape moving at a constant rate. The bottom half, which is not exposed to the air, serves as the reference. The degree of color change incurred by the top half of the tape is proportional to the phosgene concentration. Photometric comparison is made of both the upper and lower halves of the tape, and an external recorder activates an alarm if preset phosgene concentrations are exceeded (Tuggle et al., 1979).

Other methods that have been successfully used to measure phosgene in ambient air include pulsed flow coulometry (Singh et al., 1975) and ultraviolet spectroscopy (Crummett and McLean, 1965). In liquid form, phosgene can be assayed iodometrically (Beard, 1982). A review of some of the early methods of phosgene detection has been reported by the National Institute for Occupational Safety and Health (1976).

2.3 PRODUCTION, USE, AND OCCUPATIONAL EXPOSURE OF PHOSGENE

2.3.1 Production

2.3.1.1 Production Process. Phosgene is manufactured by the reaction of equimolar amounts of anhydrous chlorine and high-purity carbon monoxide in the presence of a carbon catalyst (SRI International, 1984; Hardy, 1982).

2.3.1.2 Producers and Production Volumes. Table 2-3 lists the companies which were listed by SRI International (1985) as domestic manufacturers of phosgene as of January 1, 1985.

The U.S. International Trade Commission (USITC) reported the production volumes for phosgene (U.S. International Trade Commission, 1981, 1982, 1983, 1984, 1985) shown in Table 2-4. According to SRI International (1985), the USITC production volume data are understated. In recent years, as much as 35 to 40 percent of the total phosgene produced has not been reported by some producers because all of their production is captively used (SRI International, 1984).

2.3.2 Use

Phosgene is a widely used chemical intermediate. It is usually produced and used captively at the point of production. In 1981, production of toluene diisocyanate (TDI) accounted for 51 percent of the phosgene used. The remainder was used in the production of polymethylene polyphenylisocyanate (33 percent), polycarbonate resins (9 percent), and other miscellaneous applications (7 percent), including use in the synthesis of chloroformate and carbonate chemical intermediates (SRI International, 1984; Hardy, 1982). Estimates of phosgene consumption (in millions of pounds) by end product application are shown below (SRI International, 1984).

Year	TDI	Polymethylene polyphenyl-isocyanate	Polycarbonate resins	Other	Total
1977	758	317	74	130	1279
1981	700	465	125	100	1390

2.3.3 Occupational Exposure

Estimates of occupational exposures to phosgene have been reported in industrial hygiene surveys performed by the National Institute for Occupational Safety and Health (NIOSH). According to the National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, 5752 workers were potentially exposed to the compound in domestic workplace environments in 1970. In 1976, NIOSH estimated that as many as 10,000 workers were potentially exposed to phosgene (National Institute for Occupational Safety and Health, 1976). Preliminary data from the National Occupational Exposure Survey (NOES), conducted by

TABLE 2-3. PHOSGENE MANUFACTURERS AND ANNUAL PRODUCTION CAPACITIES

Manufacturer	Location	Estimated annual production capacity (millions of pounds)
BASF Wyandotte Corp. Polymers Group Urethanes Chems. Business	Geismar, LA	200
Dow Chem. U.S.A.	Freeport, TX	130
E.I. du Pont de Nemours & Co., Inc. Polymer Products Dept.	Deepwater, NJ	<80
Essex Chem. Corp. Essex Indust. Chems., Inc., subsid. Organic Intermediates Dept.	Baltimore, MD	8
Gen. Electric Co. Plastics Business Operations	Mount Vernon, IN	125
ICI Americas Inc. Performances Resins Div. Rubicon Chems., Inc.	Geismar, LA	150
Mobay Chem. Corp. Polyurethane Div.	Cedar Bayou, TX	450
	New Martinsville, WV	250
Olin Corp. Olin Chems.	Lake Charles, LA	140
	Moundsville, WV	110
PPG Indust., Inc. Chems. Group	Barberton, OH	5
Specialty Products	La Porte, TX	50
Stauffer Chem. Co. Agricultural Chem. Div.	Cold Creek, AL	24
	St. Gabriel, LA	not available
Union Carbide Corp. Agricultural Products Group	Institute, WV	140
The Upjohn Co. Polymer Chems. Div.	La Porte, TX	270
Van De Mark Chem. Co., Inc.	Lockport, NY	8
	Total	<2140

Source: SRI International (1985).

TABLE 2-4. PHOSGENE ANNUAL PRODUCTION VOLUME

Year	Production volume (billion pounds)
1980	1.04
1981	1.12
1982	0.97
1983	1.05
1984	1.22

Source: U.S. International Trade Commission (1981, 1982, 1983, 1984, 1985).

NIOSH from 1980 to 1983, indicated that 2358 workers, including 282 women, were potentially exposed to phosgene in the workplace in 1980. Note that the NOES estimate represents potential exposures to the actual compound only, whereas the NOHS estimate includes potential exposure to phosgene from its precursors as well as the parent compound. The National Institute for Occupational Safety and Health document (1976) did not explain how the estimate of 10,000 potentially exposed workers was derived.

The current TWA-TLV for phosgene exposure in the workplace is 0.1 ppm (0.4 mg/m^3) (American Conference of Governmental Industrial Hygienists, 1985). This same level, 0.1 ppm, has also been adopted by the Occupational Safety and Health Administration (OSHA) as an 8-hour time-weighted average permissible exposure limit for phosgene (Code of Federal Regulations, 1983). The current TWA-TLV was first adopted by the American Conference of Governmental Industrial Hygienists in 1966 (American Conference of Governmental Industrial Hygienists, 1966).

A list of the current standards for phosgene in several countries is presented in Table 2-5. The Eastern European countries adopted their standards from the U.S.S.R., while Japan, West Germany, and Great Britain adopted standards identical to those recommended by ACGIH (National Institute for Occupational Safety and Health, 1976).

Cucinell (1974) reviewed the literature on the effects of subchronic exposure of animals to phosgene and suggested that the TWA-TLV for phosgene in the workplace be 0.02 ppm. This was based mainly on the work of Cameron et al. (1942) who showed that exposure to phosgene at a concentration of 0.2 ppm for 5 hours/day for 5 consecutive days produced evidence of pulmonary edema in 41 percent of the test animals (goats, cats, rabbits, guinea pigs, rats, mice). Using additional safety factors, Cucinell also suggested that the highest

TABLE 2-5. MAXIMUM ALLOWABLE CONCENTRATION VALUES FOR PHOSGENE IN SEVERAL COUNTRIES

Country	Maximum allowable concentrations	
	ppm	mg/m³
Bulgaria	0.125	0.5
Czechoslovakia	0.5	2
Czechoslovakia	1.0[a]	4[a]
Egypt	1.0	4
Finland	1.0	4
Germany, East	0.125	0.5
Germany, West	0.1	0.4
Great Britain	0.1	0.4
Hungary	0.125	0.5
Japan	0.1	0.4
Poland	0.125	0.5
Romania	0.125	0.5
Sweden	0.05[a]	0.2[a]
United States	0.1	0.4
U.S.S.R.	0.125	0.5
Yugoslavia	0.1	0.4

[a] Ceiling limit for a short single exposure.

Source: National Institute for Occupational Safety and Health (1976); Winell (1975).

phosgene level in ambient air that would be safe for all humans to breathe 24 hours a day is 600 ppt. This concentration is ten times higher than the highest phosgene concentration measured in ambient air (61.1 ppt over Los Angeles; Singh et al., 1977).

An accidental release of phosgene is not the only potential source of this gas in the workplace. Various chlorinated hydrocarbons can decompose during welding or when in contact with a flame or a hot carbon or metal surface to yield phosgene. Gerritsen and Buschmann (1960) showed that methylene chloride would decompose to form toxic levels of phosgene under possible working conditions. The authors treated a painted wood surface (0.3 m^2) with a commercial chemical paint remover that contained 92 percent of a volatile solvent consisting almost entirely of methylene chloride with small amounts of ethanol and trichloroethylene. Approximately 50 g of the paint remover was applied to the surface. The wood was then placed in a large cupboard (6 m^3) that contained a burning kerosene stove. Phosgene levels were determined at frequent intervals using two different analytical techniques. Potentially lethal levels of phosgene (up to 128 ppm) were generated after only ten minutes. The authors also reported two cases of phosgene poisoning, one of which was fatal, under circumstances similar to their test conditions.

The generation of phosgene due to the decomposition of chlorinated hydrocarbons during welding has also been well established. Birgesson (1982) described the hazard of exposure to the pyrolysis products of Freon, especially phosgene, encountered by welders working in cold storage rooms. Rinzema and Silverstein (1972) and Rinzema (1971) measured the phosgene generated by various welding techniques in the presence of several individual chlorinated hydrocarbons. They concluded that chloroform, carbon tetrachloride, ethylene dichloride, methyl chloroform, and o-dichlorobenzene did not decompose under common welding conditions to yield toxic levels of phosgene. Trichloroethylene and perchloroethylene, however, did undergo extensive decomposition. The authors concluded that hazardous levels of phosgene could be generated by welding in the presence of the latter two solvents. However, the analytical technique used to quantify phosgene in these studies was susceptible to interferences from acyl chlorides and acetyl chlorides.

Andersson et al. (1975) and Dahlberg and Myrin (1971) performed similar experiments to measure the decomposition products of trichloroethylene and perchloroethylene using various welding techniques. Phosgene levels were measured by gas chromatography, an analytical method that is not subject to interferences from other structurally related compounds. It was found that short-wave (UV) radiation generated by the welding arcs caused both trichloroethylene and perchloroethylene to decompose to form phosgene. However, dichloroacetyl chloride was formed five times as fast as phosgene when atmospheres containing trichloroethylene, but not perchloroethylene, were exposed to welding. The authors concluded that perchloroethylene posed a greater hazard to welders than trichloroethylene. Nonetheless, there are several published reports of phosgene intoxication in welders working in the presence of trichloroethylene.

Noweir et al. (1973b) demonstrated that, under certain conditions, toxic levels of phosgene can be generated by the combustion of carbon tetrachloride. In one experiment, carbon tetrachloride (10.2 ppm) was combusted in an animal inhalation chamber and the pyrolysis products were determined to be phosgene, 10.15 ppm; chlorine, 7.2 ppm; chlorine dioxide, 0.6 ppm; other, 5.5 ppm.

Another source of phosgene generation is via the combustion of polyvinylchloride (PVC). Brown and Birky (1980) measured the generation of phosgene after the thermal decomposition of PVC by four different methods: (1) thermal degradation of PVC in a resistively heated furnace, (2) electrical overloading of a PVC-clad wire, (3) electrical arcing between electrodes partially covered with PVC, and (4) electric-arc initiated flaming combustion in a cup furnace. Phosgene levels were analyzed and quantified using gas chromatography, infrared spectroscopy, and mass spectroscopy. The authors demonstrated that significant quantities of phosgene were generated from PVC by the electric arc method (30-50 ppm), and lesser quantities were formed in the other scenarios (0.5-1.3 ppm). Bjerre (1984) also demonstrated that toxic levels of phosgene could be generated from the thermal decomposition of PVC and summarized the optimal conditions for its formation: (1) PVC combustion takes place in an intermediate temperature region at a probable lower limit of 500°C and with a limited excess of oxygen; (2) the gases of combustion keep a temperature between 330 and 600°C for the longest possible period of time; and (3) the gases are, at the same time, in contact with hot surfaces, e.g., copper, iron, activated carbon, that act as catalysts. Phosgene was not detected as a combustion product of several polyurethane-ether foams (Paulson and Moran, 1974).

2.4 ATMOSPHERIC LEVELS AND FATE OF PHOSGENE

Measurable quantities of phosgene have been found in ambient air, but not in water, because phosgene decomposes in water immediately after going into solution.

2.4.1 Atmospheric Levels

Ambient air concentrations of phosgene have been attributed to three main sources: (1) direct emissions of phosgene during its manufacture, handling, and use; (2) thermal decomposition of chlorinated hydrocarbons; and (3) photooxidation of chloroethylenes in the air. The first two sources are generally contained, and although they pose a significant indoor hazard, they constitute only a negligible contribution to the environmental concentrations (Singh, 1976). Of far greater consequence is the photochemical oxidation of chloroethylenes. The two major chloroethylenes that contribute to the atmospheric pool of phosgene are perchloroethylene and trichloroethylene. In 1975 alone, it was estimated that 1.5 x 10^6 tons of these compounds were released into the world's environment. At that rate, Singh (1976) estimated that those emissions could result in the formation of about 3.0 x 10^5 tons of phosgene per year.

The photooxidation of trichloroethylene and perchloroethylene to phosgene (and other compounds) was demonstrated experimentally by Gay et al. (1976). The compounds, at 3.45 to 5.0 ppm, were photooxidized in air with ultraviolet light (wavelength not reported) in the presence of nitrogen dioxide. Analyses were performed by long-path infrared spectroscopy and wet chemical and chemiluminescent procedures. Under these conditions, 66 percent of the trichloroethylene and 7 percent of the perchloroethylene samples were degraded after 140 minutes of irradiation, yielding phosgene concentrations of 0.47 and 0.12 ppm, respectively. Of the other compounds studied, 1,1-dichloroethylene was also photooxidized to phosgene, but ethylene, vinyl chloride, and 1,2-dichloroethylene did not yield phosgene, although these compounds were extensively photooxidized under the test conditions. The authors proposed a reaction sequence that involves photolysis of nitrogen dioxide to form ozone, which reacts with the double bond to form an unstable epoxide. The epoxide rearranges through chlorine atom movement to yield phosgene and other products. Dilling et al. (1976) also indicated that phosgene, in the presence of nitrous oxide, increased the degradation rate of trichloroethylene.

Phosgene levels have been measured in ambient air by a group of researchers in California (Brodzinsky and Singh, 1983; Singh et al., 1977; Singh, 1976). All monitoring was conducted on a 24-hour basis using a gas chromatograph equipped with two electron-capture detectors in series. Calibrations were performed using a permeation tube and were checked in the field using absolute pulse flow coulometry. Data on measurements taken at four different locations in California are presented in Table 2-6. In rural areas, phosgene was present at an average concentration of 21.7 ppt, while in urban areas the average was 31.8 ppt. The highest concentration measured by the researchers was 61.1 ppt in Los Angeles, although it was suggested that higher concentrations could occur under highly stagnant weather conditions (Singh et al., 1977). The authors also stated that the relatively smaller differences in phosgene concentrations between urban and remote locations (about 30 percent) as compared to the bigger differences for its precursors (twentyfold) was an indication of the relative stability of phosgene in the troposphere, and that

TABLE 2-6. ATMOSPHERIC LEVELS OF PHOSGENE AND ITS PRECURSORS AT SELECTED SITES IN CALIFORNIA

		Concentrations of compounds detected (ppt)[a]		
Location	Site characterization	Phosgene	Perchloroethylene	Trichloroethylene
Badger Pass	Remote	21.7±5.2 (13.3-28.9)	30.7±10.5 (15.4-92.1)	15.6 2.5 (14.4-21.6)
Los Angeles	Urban	31.8±8.3 (21.1-61.1)	674.4±498.7 (60-8-2267.3)	312.6 302.3 (25.5-1772.3)
Menlo Park	Urban-suburban	30.3±3.1 (27.8-38.9)	201.9±413.9 (16.0-2490.0)	113.5±528.1 (10.0-5490.0)
Palm Springs	Downwind of Los Angeles	29.3±6.2 (16.7-44.4)	278.2±232.6 (17.7-1153.1)	39.7±83.6 (12.8-828.8)

[a] Values represent mean concentrations ± S.D. of multiple samplings (n = 10-257).

Source: Singh et al. (1977).

its precursors are well distributed in the atmosphere before any significant conversion to phosgene occurs.

Fenceline monitoring with colorimetric indicator badges (sensitive to about 0.01 ppm) at one phosgene production plant revealed no color changes (Diller, 1986).

2.4.2 Atmospheric Fate

Preliminary studies on the atmospheric fate of phosgene suggest that phosgene is not eliminated through gas-phase hydrolysis as was commonly believed. When present in a cloud chamber at 10 ppm and 100 percent relative humidity, phosgene decomposition at various temperatures is only slightly enhanced compared to the decomposition of 10 ppm phosgene in dry air (Noweir et al., 1973a). Gay et al. (1976) and Singh et al. (1975) confirmed these findings: The known absorption cross-section of phosgene and smog-chamber studies (where 1-5 ppm phosgene was stable for 15 hours under simulated tropospheric irradiations in the presence of 10,000 ppm of water vapor) suggested negligible tropospheric loss through photolysis and gas-phase hydrolysis. Butler and Snelson (1979) calculated a half-life for the homogeneous gas-phase hydrolysis of 1 ppb phosgene in the atmosphere to be between 20 and 630 years. Other gas-phase reactions involving O· and OH· radicals are also very slow (Singh, 1976).

The two important sinks for the removal of phosgene from the ambient air appear to be heterogeneous decomposition and slow liquid-phase hydrolysis. The importance of heterogeneous decomposition has been confirmed by findings that showed that low concentrations of phosgene were destroyed shortly after contact with most surfaces, especially at elevated temperatures, i.e., 200 to 900°C (Noweir et al., 1973a). At normal atmospheric temperatures, however, liquid-phase hydrolysis appears to be a more significant sink. At a Palm Springs site, a 15 to 20 percent decline in the ambient air concentration of phosgene was measured following intermittent rainfall that lasted from 50 to 60 hours (Singh et al., 1977). Because of the existence of at least two major tropospheric sinks, Singh et al. (1977) concluded that no possibility exists for any significant stratospheric impact, i.e., destruction of the ozone layer, due to phosgene.

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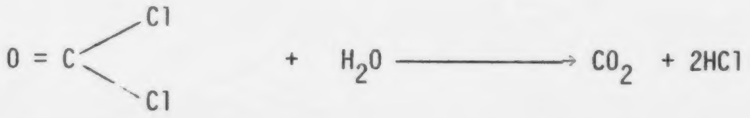
3. PHOSGENE METABOLISM AND MECHANISMS OF ACTION

3.1 PHOSGENE METABOLISM

3.1.1 Chemistry and Biochemistry

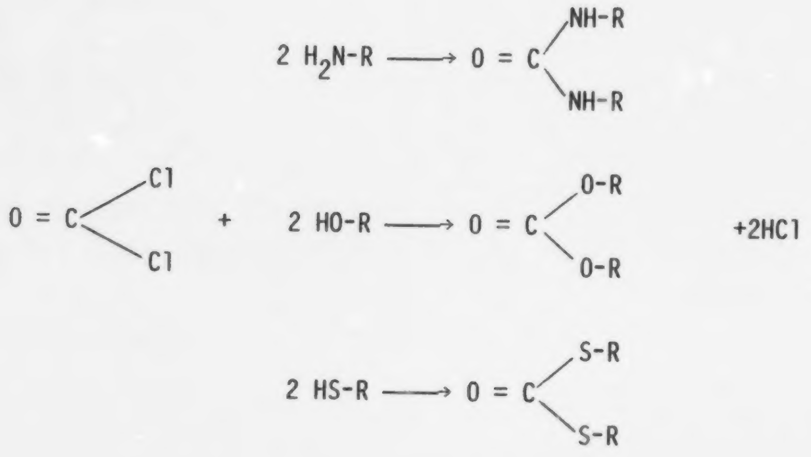
There are no adequate reports in the literature on the *in vivo* or *in vitro* metabolism of phosgene. Therefore, our limited knowledge of the interactions of molecular phosgene once in contact with living organisms comes from chemical and biochemical studies. Phosgene gas is only slightly soluble in water. Nash and Pattle (1971) bubbled phosgene (10-20 ppm in dry air) at a flow rate of 0.6 liters per minute through 4 mL of water for 30 seconds. Under these conditions only 15 to 20 percent of the phosgene was absorbed. Absorption was unchanged in neutral buffer or acid solutions, but was increased in alkaline, solutions and increased still more in solutions containing non-ionized amines, phenoxide ions, or sulfite.

Once dissolved in water, phosgene is rapidly hydrolyzed to form carbon dioxide and hydrochloric acid (HCl):



The reaction rate is so fast that early investigators could not measure it (Rona, 1921). Later, the pseudo-first-order rate constants for the hydrolysis of phosgene at 35 and 45.5°C were measured to be 26.7 and 75 sec^{-1}, respectively (Manogue and Pigford, 1960). From these data, a half-life for the hydrolysis of phosgene at 37°C can be calculated to be 0.026 seconds.

Despite the rapid rate of reaction with water, it has been demonstrated that phosgene reacts even more rapidly with other functional groups. Potts et al. (1949) reacted diphosgene, trichloromethylchloroformate, with aqueous solutions of a number of compounds. Diphosgene was used instead of phosgene because it was easier to handle and diphosgene has been reported to possess chemical and toxicological reactivities indistinguishable from those of phosgene (Potts et al., 1949; Bruner and Coman, 1945). After the reaction of diphosgene with the test solution was complete, the amount of liberated gas was measured. Since only the reaction with water would yield gas, a reduction in gas production was considered to indicate that the carbonyl group had reacted with the solute. Compounds with free amino, hydrazino, sulfhydryl, and hydroxy groups were found to be acylated by diphosgene in the presence of large excesses of water. Hexamethylenetetramine, aniline, p-aminobenzoic acid, and cysteine all bound 80 percent or more of the diphosgene carbonyl groups. The acylation reactions of phosgene with -NH_2, -OH, and -SH groups are shown below (Gerard, 1948):



Biochemical studies have also indicated that phosgene can acylate tissue macromolecules. Cessi et al. (1966) allowed 20 mg of poly-L-lysine to react with 10 mg of [^{14}C]phosgene (0.1 mCi) dissolved in a small amount of tetrahydrofuran. Human serum albumin (100 mg) was also reacted with 0.2 mCi of [^{14}C]phosgene in a similar manner. Both reactions yielded highly labeled derivatives. Enzymatic hydrolysis of the serum albumin derivatives, followed by amino acid analysis of the resultant labeled peptides, indicated that phosgene bound to the ε-amino groups of proteins.

The acylating properties of phosgene have given rise to some questions of the potential carcinogenicity of phosgene. When phosgene and cysteine are chemically reacted, a stable adduct identified as 2-oxothiazolidine-4-carboxylic acid (4-carboxy-thiazolidine-2-one) is formed (Mansuy et al., 1977). This same adduct is also formed when chloroform (Mansuy et al., 1977; Pohl et al., 1977) or carbon tetrachloride (Shah et al., 1979) is incubated with rat hepatic microsomes in the presence of cysteine. Both chloroform and carbon tetrachloride are demonstrated animal carcinogens (Eschenbrenner and Miller, 1944; International Agency for Research on Cancer, 1971). One current theory is that cytochrome P-450-mediated metabolism of these compounds produces metabolites, one of which is phosgene, that form stable adducts with cellular macromolecules, leading to carcinogenesis (U.S. Environmental Protection Agency, 1984, 1985). However, there are no acceptable studies in the literature that test the potential carcinogenicity of phosgene in laboratory animals (see Section 5.3.2 for details).

3.1.2 Absorption and Distribution

It is generally accepted that unreacted phosgene does not get past the pulmonary circulation. Using the solubility and hydrolysis rate of phosgene in water as determined by Manogue and Pigford (1960) and Hall (unpublished), a phosgene exposure concentration of 25 ppm, and published values for the thickness of the blood-air barrier (1 μM), capillary diameter (8 μM), and blood residence time in the capillaries (1 sec); Nash and Pattle (1971) calculated that phosgene would mainly diffuse undecomposed through the blood-air barrier into the blood, but that only a small portion would leave the capillaries undecomposed. However, the percentage actually entering the capillaries would probably be much less than implied above because both the solubility and decomposition of phosgene are increased by the presence of biologically important chemical groups (Nash and Pattle, 1971). In an abstract by Slade et al. (1983), a study was described in which mice, rats, hamsters, guinea pigs, and rabbits were exposed by inhalation to [^{14}C]phosgene at 1.6 ppm for 3 minutes. [^{14}C] was detected at very low levels in blood and liver samples of all animals. However, this study is of limited value because the [^{14}C] labeled compounds were not identified.

Gerard (1948) presented the findings of several studies that indirectly demonstrate that significant levels of phosgene do not get past the lung. In one study, a plug was placed in a main bronchus of a dog and the animal was exposed to phosgene at a level "far exceeding the normal lethal dose." The plug was then removed from the protected lobe and placed in the other bronchus (to keep edema fluid from spilling over). The dog did not die from this exposure despite extreme pathology in the exposed lung and the loss of large quantities of plasma fluid. Other studies, in which one dog was exposed to phosgene and a second dog received blood from the exposed dog (either by transfusion or crossed circulation) without adverse effect, also indicate that undecomposed phosgene does not enter the general circulation.

3.2 MECHANISMS OF ACTION

3.2.1 Hydrolysis Versus Acylation

Although the effects of phosgene in animals have been studied extensively for many years, the exact mechanisms of action remain elusive. It was believed at one time that phosgene owed its toxicity to the property of being hydrolyzed in the presence of water to HCl and CO_2 (Winternitz et al., 1920). Although it was understood that the effects of inhalation of HCl and phosgene are different, the difference was ascribed to the fact that HCl strikes first and hardest at the larynx and trachea, damaging less the distal portion of the respiratory tract, i.e., the bronchioles and pulmonary alveoli. With phosgene, on the other hand, little decomposition takes place until the gas reaches the lungs, where, in the smaller bronchi and in the alveoli, it comes into contact with sufficient water vapor to bring about the evolution of HCl. This would explain the severe damage produced by phosgene in the lower air passages rather than in the trachea and bronchi.

It is now believed that the pathology observed with phosgene inhalation is mainly a result of the acylating properties of phosgene, although HCl production may play a minor role, especially in high-level exposures (Diller, 1985). Nash and Pattle (1971) calculated the maximum concentration (C) of hydrochloric acid which would be produced in a tissue if a molar concentration (C_1) of phosgene were present in the gas in contact with a slab of tissue of thickness (b) in which phosgene has a diffusion coefficient (D) and was hydrolyzed with a rate defined by a constant (k) using the following formula:

$$C = \lambda C_1 b^2 \; k/D_2$$

where (D_2) is the diffusion coefficient of acid in the tissue. Using the solubility (λ) and hydrolysis (k) values of Manogue and Pigford (1960), the maximum concentration of acid in a blood-air barrier of thickness 1 μm in contact with 25 ppm of phosgene is 7×10^{-10}M, which is negligible. It was concluded that HCl production could not account for the toxicity seen with exposures to phosgene at 25 ppm.

Additional evidence for acylation over hydrolysis as the major mechanism of phosgene's toxicity was provided by Potts et al. (1949). Rats and mice were exposed to ketene ($H_2C=C=O$) at 0.5 mg/L for 1.5 minutes. Seven of eight mice died within 0.5 to 24 hours (rat mortality not reported), and showed clinical symptoms similar to those seen in phosgene exposures. Sections of the lungs of these animals were given to a pathologist as unknowns and were reported by him as "severe phosgene poisoning." Ketene, like phosgene, can acylate the free amino groups of protein in solution, but unlike phosgene does not hydrolyze to form a strong acid. Finally, substances that protect prophylactically against phosgene poisoning (hexamethylenetetramine, free amines, and thromboplastin) do not protect against HCl poisoning (Diller, 1985).

3.2.2 Subcellular Biochemical Mechanisms

Frosolono and Pawlowski (1977) have extended the studies on phosgene to obtain information on the biochemical mechanisms of phosgene damage in the lung at the organelle and enzymatic levels. Because of its pronounced chemical reactivity, the authors speculated that phosgene might inhibit a broad spectrum of pulmonary enzyme systems, disrupting the basic metabolism of the lung and producing profound effects upon the integrity of the tissues (Potts et al., 1949). Male rats (CFE Carworth) were exposed for the most part to phosgene at 100 ppm for 10 minutes (1000 ppm-min), although exposures as high as 4300 ppm-min were also used. Most exposures were for ten minutes. Groups of animals were killed at 0, 30, and 60 minutes postexposure, and lungs taken for biochemical determinations. The extent of pulmonary edema was also determined for comparison purposes. Lungs were fractionated into four major subcellular organelle fractions: nuclear debris, mitochondrial-lysosomal, microsomal, and soluble (cytoplasmic). Activities of p-nitrophenyl phosphatase, cytochrome C oxidase, ATPase, and lactic dehydrogenase within these fractions were found to be decreased (generally 10-80 percent) at all intervals after exposure. There was a corresponding increase in protein concentration in all fractions, which was particularly marked in the soluble fraction. Lactic dehydrogenase levels in serum rose with time after exposure, with a concomitant fall of the enzyme level in the tissue homogenate and soluble fractions. Pulmonary edema, as indicated by an increased water content in the lung, was not evident at 30 minutes, but there was a 5 percent increase in water content at 60 minutes. Based on these results, the authors suggested that one possible mechanism playing a role in phosgene damage may be associated with either inhibition or loss of enzyme activity in the lung.

In a companion paper, Pawlowski and Frosolono (1977) evaluated ultrastructural alterations in rat lungs by electron microscopy, attempting to correlate them with their biochemical observations (Frosolono and Pawlowski, 1977). Exposure conditions were the same as described for the biochemical studies. The investigation was limited to those events that took place in the terminal bronchoalveolar region. The earliest morphologic result of phosgene damage, seen immediately after exposure, was a vesiculation of cells in the terminal bronchiolar epithelium, and most probably represented the beginning of edema in these cells. This was followed by septal extracellular edema with minimal intracellular edema. Intracellular edema developed next and led to cellular disruption and necrosis. Fluid appeared in the alveoli after the intracellular and extracellular interstitial spaces of the septa became very swollen. Interstitial cells seemed to be very susceptible to the effects of edema. Whether these cells are the specific targets of phosgene chemical reaction remains to be determined. However, because of the decreases in enzyme activity, the authors suggested that metabolic depression and disturbances may precede major ultrastructural changes in the alveolar region.

In a recent biochemical study, Currie et al. (1985) determined the effects of phosgene on pulmonary energy metabolism. Male Sprague-Dawley rats were exposed to 1 ppm phosgene for 4 hours (CT = 240 ppm-min). Lungs were obtained at the end of the 4-hour exposure and at 24-hour intervals thereafter over a 4-day period for histological and biochemical assessments to correlate the onset of pulmonary edema with changes in energy metabolism. Edema was estimated by histologic methods and by measurement of lung wet and dry weights. In parallel studies, mitochondrial oxygen uptake or respiratory activity was measured using oxygen electrodes. The respiratory control ratio or State 3/State 4 ratio is a sensitive measure of mitochondrial structural integrity and was used as an indicator of damage to the mitochondrial electron transport chain. The investigators observed that the significant reduction in the respiratory control index, found immediately following phosgene exposure, coincided with the highest level of percent water in the lung. There was a concomitant decrease in ATP concentration, based on mmol ATP/g wet weight of lung, that persisted on the third day after exposure. The authors concluded that reductions in ATP levels and in Na-K-ATPase activity may play a major role in damage to lung tissue after exposure to phosgene.

Frosolono and Currie (1985), reasoning that the maintenance of alveolar structural integrity, essential for exchange of respiratory gases, is dependent upon reduction of alveolar surface tension forces by the integrated function of pulmonary surfactant system constituents, determined the response of the pulmonary surfactant system to phosgene. The animals used and the phosgene exposure conditions were similar to those described in their energy metabolism studies (Currie et al., 1985). Immediately upon termination of phosgene exposure, microsomal protein and palmitoyl transferase activity were reduced roughly 20 percent below normal values, and lung wet weight, used as a measure of edema, was elevated approximately 20 percent above control levels. From the first through the third day after exposure, all measured parameters except the phosphatidylinositol constituent of the surfactant fraction were increased above control values. In general, maximum levels were observed on the second day; however, the palmitoyl transferase activity and surfactant concentration continued to increase on the third day. Based on these results, the authors suggested that (1) components of the pulmonary surfactant system may be involved in maintenance of pulmonary fluid balance, and (2) the presence of excess water in the lungs as a result of phosgene exposure may represent a signal for increased synthesis of antiedematogenic materials (surfactant) to promote removal of inappropriate fluid.

3.2.3 Role of the Nervous System

Because of the bradycardia, salivation, vomiting, urination, and defecation regularly occurring in animals exposed to phosgene, all suggestive of abnormally high parasympathetic tone, Bruner et al. (1948) investigated neurogenic involvement following phosgene exposure in an electrocardiographic study. Thirteen healthy dogs were exposed to either 0.5 mg/L (125 ppm) phosgene for 30 minutes or 5.0 mg/L (1250 ppm) for 3 minutes. Both exposures are an $L(CT)_{99}$ for dogs. Electrocardiography during or shortly after gassing showed a combination of sinus arrhythmia, sinus bradycardia, and prolonged conduction time related to heightened vagal activity. These changes regressed to normal values as the heart rate increased during the second to sixth hour, and showed no further change despite subsequent development of tachycardia coincident with development of pulmonary edema, anoxemia, and circulatory shock. No correlation could be discovered between changes of electrocardiographic measurements and either the rate of development or severity of the effects of phosgene poisoning. In dogs in which the vagi were cut or blocked before or after gassing, or in which the end organs were blocked by the administration of atropine, the bradycardia was absent, but no change was produced in the pulmonary response to phosgene. The authors concluded that the early bradycardia of experimental phosgene poisoning was mediated by efferent vagal fibers, but that the vagal efferent fiber to the lung and afferents from the lung, trachea, and larynx have little, if anything, to do with the pulmonary tissue's response to phosgene.

Ivanhoe and Meyers (1964) put forward the hypothesis that the pulmonary edema induced by phosgene may be related to hypoactive sympathetic activity. These investigators exposed 8 adult male and 2 adult female New Zealand rabbits to phosgene doses ranging from 50 ppm for 14 minutes to 200 ppm for 25 minutes. Changes in the total electrical activity of the cervical sympathetic nerve before and after the animals had been gassed were measured. The animals that survived four hours after exposure were sacrificed at that time, and the lungs examined. The exposure to overwhelming concentrations of phosgene was followed by an immediate marked drop in total recorded electrical activity of the cervical sympathetic nerve in six of the ten animals, a change that usually occurred during exposure and never more than 20 minutes after its termination. On several occasions, great increases in urinary bladder and intestinal peristaltic activity were observed in the gassed animals, coincidental with the drop in electrical nerve activity. Gross observations of the lungs at the end of the experiment revealed congestive changes of the patchy hyperemia type, characteristic of neuroparalytic acute pulmonary edema. Assuming that the abrupt sharp drop in the electrical activity of the right cervical sympathetic nerves that followed phosgene gassing in the rabbits reflects a similar and coincident fall in sympathetic tone everywhere else in the organisms, including the lung, and considering the fact that the patchy hyperemia was still in its first stages of development at a time when the neural effects had already occurred, the authors suggested a cause-and-effect relationship between the fall in sympathetic activity and a vascular dynamic disturbance in the lung leading to edema.

In this regard, the authors call attention to the observations of other researchers, which could be interpreted as manifestations of reduced sympathetic activity following exposure to phosgene, such as the bradycardia and systemic arterial hypotension observed by Patt et al. (1946) and the increased motor activity of the bladder and intestinal tract observed by Coman et al. (1947). However, the authors' conclusions should be viewed skeptically because only 60 percent of the animals showed a drop in electrical activity.

3.3 SUMMARY

Although in vivo and in vitro studies on the metabolism of phosgene have not been performed, chemical and biochemical data, as well as indirect animal studies, aid in the understanding of several aspects of phosgene metabolism and its mechanisms of action. Phosgene reacts rapidly with water, but more rapidly with certain chemical groups found in tissue macromolecules, such as free amines and sulfhydryls. Because of its high reactivity, it is doubtful that any unreacted phosgene will enter the general circulation even after exposure to high concentrations of the gas. The pathology of phosgene poisoning is mainly due to its acylating properties and not a result of HCl generation upon hydrolysis, although HCl production may play a minor role. The production of pulmonary edema following phosgene exposure has been correlated with reductions in pulmonary ATP levels and Na-K-ATPase activity, as well as inhibition of other pulmonary enzymes. The role of the nervous system in the toxicity of phosgene is considered to be a nonspecific effect of irritant gases (Diller, 1985).

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4. ACUTE TOXICITY OF PHOSGENE EXPOSURE IN ANIMALS AND HUMANS

4.1 ANIMAL STUDIES

Animal studies on phosgene were initially undertaken because of its use as a chemical warfare agent in World War I. As used during the war, phosgene produced its noxious effects in humans through inhalation. Consequently, animal studies were also conducted using the inhalation route of administration, and essentially all studies on the effects of phosgene in animals have been carried out via this route.

The effects of acute exposure of animals to phosgene, summarized in Table 4-1, are based largely on the data presented by Diller and Zante (1982). Extrapolating from the data in their tables, Diller and Zante proposed an approximate $L(CT)_{50}$ for a number of species and ranked them according to their susceptibility to acute phosgene toxicity as shown in Table 4-2.

4.1.1 Measurement of Phosgene Exposure

The magnitude of exposure to a toxic gas or vapor is determined by the concentration of the toxic component (C) and the duration of exposure (time, T). In comparing the lethalities of potential war gases, Haber (1924) introduced the concept of a "death product," expressed as the product of the concentration and exposure time. This was later postulated as "Haber's Law," which in its general form states that the product of the concentration and time of exposure required to produce a specific physiologic effect is equal to a constant, or CT = K. Although this law generally applies to physiological effects, the effect observed by early investigators was death.

The validity of the CT = K relationship for phosgene poisoning was tested by Flury (1921). Twenty cats were exposed to phosgene concentrations ranging from 5 to 500 mg/m^3 for 0.5 to 120 minutes (CT values ranged from 37.5 to 562 ppm-min). When K (death or survival) was plotted as a function of C (ordinate) and T (abscissa), the curve that best fit the data was a hyperbola, as

TABLE 4-1. EFFECTS OF ACUTE AND REPEATED INHALATION EXPOSURES OF ANIMALS TO PHOSGENE

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Single Exposures					
Mouse	ns	ns/ns	225 ppm-min (15 ppm x 15 min)	$L(CT)_{50}$	Cameron and Foss (1941)
Mouse	ns	ns/ns	750 ppm-min	$L(CT)_{50}$	Gerard (1948)
Mouse	-	-	850 ppm-min (850 ppm x 1 min)	$L(CT)_{50}$	Chasis (1944)[b]
Mouse	-	-	3300 ppm-min (3300 ppm x 1 min)	$L(CT)_{50}$	Moor and Gates (1946)[b]
Mouse	ns	ns/ns	42,500 ppm-min (4250 ppm x 10 min)	Death within 5 min	Swift and Postel (1945)
Mouse	ns	ns/ns	Pure phosgene (CT not indicated)	Death within 30-60 min	Laqueur and Magnus (1921)
Rat	Wistar	4/M	15 ppm-min (3 ppm x 5 min)	Slight to moderate chronic pneumonitis	Gross et al. (1965)
Rat	Wistar	8/M	30 ppm-min (1 ppm x 30 min)	Lowered CO-diffusion capacity	Long and Hatch (1961)
Rat	ChR-CD	10/M	48 ppm-min (0.2 ppm x 240 min)	No histological effect	Terrill (1976)
Rat	ns	ns	50 ppm-min	L(CT) minimum	Lohs (1963)
Rat	Wistar	15/M	50 ppm-min (0.15 ppm x 330 min)	Increase in pulmonary lavage protein content	Diller et al. (1985)
Rat	Wistar	10/M	50 ppm-min (5 ppm x 10 min)	Initiation of alveolar edema	Diller et al. (1985)
Rat	Wistar	ns/M	180 ppm-min (4 ppm x 45 min)	$L(CT)_{0}$	Rinehart and Hatch (1964)
Rat	Sprague-Dawley	20/M	240 ppm-min (1 ppm x 240 min)	Alveolar septal thickening and excess fluid and fibrin in alveolar spaces	Currie et al. (1985)
Rat	ChR-CD	10/M	240 ppm-min (1 ppm x 240 min)	No histological effects	Terrill (1976)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Rat	-	-	260 ppm-min (8.6 ppm x 30 min)	Sublethal	Marly (1970)[b]
Rat	Wistar	ns/M	300 ppm-min (4 ppm x 75 min)	$L(CT)_{50}$	Rinehart and Hatch (1964)
Rat	-	-	300 ppm-min (15 ppm x 20 min)	$L(CT)_{50}$	Kimmerle and Diller (1977)[b]
Rat	Wistar	40/ns	300-450 ppm-min (10-15 ppm x 30 min)	$L(CT)_{75}$	Henschler and Laux (1960)
Rat	-	-	350 ppm-min (35 ppm x 10 min)	$L(CT)_{20}$	Shils (1943)[b]
Rat	-	-	360 ppm-min (12 ppm x 30 min)	$L(CT)_{50}$	Chasis (1944)[b]
Rat	-	-	400 ppm-min (40 ppm x 10 min)	$L(CT)_{70}$	Kimmerle and Diller (1977)[b]
Rat	ns	44/ns	380-750 ppm-min (38-75 ppm x 10 min)	$L(CT)_{50}$	Box and Cullumbine (1947)
Rat	ns	ns/ns	500 ppm-min (25 ppm x 20 min)	$L(CT)_{50}$	Rothlin (1941)
Rat	ns	ns/ns	500 ppm-min	$L(CT)_{50}$	Gerard (1948)
Rat	Wistar	40/ns	500 ppm-min (25 ppm x 20 min)	$L(CT)_{50}$	Henschler and Laux (1960)
Rat	-	-	500 ppm-min (4 ppm x 125 min)	$L(CT)_{100}$	Rinehart (1962)[b]
Rat	ns	ns/ns	525 ppm-min (35 ppm x 15 min)	$L(CT)_{50}$	Cameron and Foss (1941)
Rat	-	-	600 ppm-min (60 ppm x 10 min)	$L(CT)_{40}$	Shils (1943)[b]
Rat	ns	ns/ns	660 ppm-min (22 ppm x 30 min) (220 ppm x 3 min)	$L(CT)_{100}$	Winternitz et al. (1920)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Rat	ns	ns/ns	740 ppm-min (37 ppm x 20 min)	$L(CT)_{100}$	Rothlin (1941)
Rat	ns	10/ns	949 ppm-min (73 ppm x 13 min)	$L(CT)_{100}$	Schultz (1945)
Rat	ns	32/ns	390-1030 ppm-min (39-103 ppm x 10 min)	$L(CT)_{75}$	Box and Cullumbire (1947)
Rat	-	-	900 ppm-min (85 ppm x 12 min)	$L(CT)_{60}$	Shils (1943)[b]
Rat	Wistar	ns/ns	800-1140 ppm-min (20-300 ppm x 3.5-57 min)	$L(CT)_{90-100}$	Coman et al. (1947)
Rat	ns	12/ns	1470 ppm-min (147 ppm x 10 min)	$L(CT)_{100}$	Box and Cullumbine (1947)
Rat	-	-	1625 ppm-min (1625 ppm x 1 min)	$L(CT)_{50}$	Chasis (1944)[b]
Rat	ns	ns/ns	2010 ppm-min (67 ppm x 30 min)	Mean survival time of 5 hours	Winternitz et al. (1920)
Guinea pig	ns	ns	480 ppm-min (32 ppm x 15 min)	$L(CT)_{50}$	Underhill (1920)
Guinea pig	ns	ns/ns	600-660 ppm-min (220 ppm x 3 min) (20 ppm x 30 min)	$L(CT)_{100}$	Winternitz et al. (1920)
Guinea pig	-	-	700 ppm-min (700 ppm x 1 min)	$L(CT)_{50}$	Chasis (1944)[b]
Guinea pig	Mongrel	ns	765 ppm-min (85 ppm x 9 min)	$L(CT)_{99}$	Coman et al. (1947)
Guinea pig	ns	ns/ns	1540 ppm-min (77 ppm x 20 min)	$L(CT)_{100}$	Ong (1972)
Guinea pig	-	-	4230 ppm-min (141 ppm x 30 min)	$L(CT)_{50}$	Moor and Gates (1946)[b]

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Guinea pig	-	-	2010 ppm-min (67 ppm x 30 min)	Mean survival time of 4.5 hours	Winternitz et al. (1920)
Rabbit	-	-	30 ppm-min (1 ppm x 30 min)	Reduced ciliary activity	Calder (1942)[b]
Rabbit	ns	ns/ns	400 ppm-min (20 ppm x 20 min)	$L(CT)_{50}$	Laqueur and Magnus (1921)
Rabbit	-	-	500 ppm-min (17 ppm x 30 min)	$L(CT)_{40}$	Frosolono (1977)[b]
Rabbit	-	-	960 ppm-min (82 ppm x 12 min)	$L(CT)_{75}$	Shils (1943)[b]
Rabbit	New Zealand	8M/2F	500-5000 ppm-min (50-200 ppm x 10-25 min)	Sharp drop in sympathetic activity	Ivanhoe and Meyers (1964)
Rabbit	ns	ns/ns	2000 ppm-min	$L(CT)_{50}$	Spector (1956)
Rabbit	-	-	2000 ppm-min	Reduced mitochondria in alveolar epithelium	Short (1943)[b]
Rabbit	ns	ns/ns	2010 ppm-min (67 ppm x 30 min)	Mean survival time of 11.5 hrs.	Winternitz et al. (1920)
Rabbit	ns	8/ns	2200 ppm-min (110 ppm x 20 min)	$L(CT)_{50}$	Cameron and Courtice (1946)
Rabbit	-	-	2460 ppm-min (82 ppm x 30 min)	$L(CT)_{90}$	Shils (1943)[b]
Rabbit	-	-	2760 ppm-min (93 ppm x 30 min)	$L(CT)_{75}$	Frosolono (1976)[b]
Rabbit	ns	ns/ns	2800 ppm-min (187 ppm x 15 min)	$L(CT)_{50}$	Underhill (1920)
Rabbit	ns	28/M	3000-4020 ppm-min (100-135 ppm x 30 min)	$L(CT)_{70}$	Halpern et al. (1950)
Rabbit	-	-	3200 ppm-min (3200 ppm x 1 min)	$L(CT)_{50}$	Moor and Gates (1946)[b]
Rabbit	ns	ns/ns	3300 ppm-min (110 ppm x 30 min) (220 ppm x 15 min)	$L(CT)_{100}$	Winternitz et al. (1920)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Rabbit	ns	ns/ns	5300 ppm-min (151 ppm x 35 min)	$L(CT)_{99}$	Coman et al. (1947)
Cat	ns	ns/ns	40 ppm-min (2.5 ppm x 15 min)	Slight illness	Flury (1921)
Cat	ns	ns/ns	80 ppm-min (2.8 ppm x 30 min)	L(CT) minimum	Flury (1921)
Cat	ns	ns/ns	110 ppm-min (11 ppm x 10 min) (2.5 ppm x 45 min)	L(CT) minimum	Flury and Zernick (1931)
Cat	ns	ns/ns	165-180 ppm-min (3 ppm x 60 min) (11 ppm x 15 min)	$L(CT)_{100}$	Flury (1921)
Cat	ns	ns/ns	248 ppm-min (12.4 ppm x 20 min)	$L(CT)_{100}$	Lohs (1963)
Cat	ns	ns/ns	250 ppm-min (0.12 ppm x 2130 min)	Interstitial edema in 50% of the animals	Wirth (1936)
Cat	ns	ns/ns	250 ppm-min (25 ppm x 10 min) (12.5 ppm x 20 min	Mostly fatal	Flury (1921)
Cat	ns	ns/ns	340 ppm-min (0.46 ppm x 800 min)	Isolated occurrences of alveolar edema	Wirth (1936)
Cat	ns	ns/ns	750 ppm-min (1.8 ppm x 470 min)	No lethality	Wirth (1936)
Cat	ns	ns/ns	900 ppm-min (70 ppm x 13 min)	$L(CT)_{99}$	Coman et al. (1947)
Cat	ns	ns/ns	1200 ppm-min (80 ppm x 15 min)	$L(CT)_{50}$	Underhill (1920)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Cat	ns	ns/ns	1200-1650 ppm-min (400 ppm x 3 min) (55 ppm x 30 min)	$L(CT)_{100}$	Winternitz et al. (1920)
Cat	-	-	1482 ppm-min (1482 ppm x 1 min)	$L(CT)_{50}$	Moor and Gates (1946)[b]
Dog	-	-	450 ppm min (45 ppm x 10 min)	$L(CT)_{50}$	Kimmerle and Diller (1977)[b]
Dog	Mongrel	24/ns	900-1050 ppm-min (60-70 ppm x 15 min)	$L(CT)_{50}$	Underhill (1920)
Dog	-	-	1050 ppm-min (502 ppm x 20 min)	$L(CT)_{50}$	Chasis (1944)[b]
Dog	ns	12/ns	1100 ppm-min (110 ppm x 10 min)	$L(CT)_{25}$	Cameron and Courtice (1946)
Dog	ns	ns/ns	1650-3300 ppm-min (550 ppm x 3 min) (220 ppm x 15 min) (110 ppm x 30 min)	$L(CT)_{100}$	Winternitz et al. (1920)
Dog	-	-	2100 ppm-min (2100 ppm x 1 min)	$L(CT)_{50}$	Chasis (1944)[b]
Dog	Mongrel	18/ns	2235-2640 ppm-min (745-880 ppm x 3 min)	$L(CT)_{70}$	Coman et al. (1947)
Dog	-	-	2340 ppm-min (78 ppm x 30 min)	$L(CT)_{55}$	Postel and Swift (1945)
Dog	Mongrel	ns/ns	2200-2700 ppm-min (734 ppm x 3 min) (90 ppm x 30 min)	$L(CT)_{99}$	Coman et al. (1947)
Dog	Mongrel	8/ns	2400-3000 ppm-min (80-100 ppm x 30 min)	$L(CT)_{100}$	Meek and Eyster (1920)
Dog	ns	64/ns	2500 ppm-min (125 ppm x 20 min)	$L(CT)_{80}$	Postel and Swift (1945)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Dog	ns	94/ns	2700 ppm-min (135 ppm x 20 min)	$L(CT)_{70}$	Freeman et al. (1945a)
Dog	ns	ns/ns	2750 ppm-min	$L(CT)_{50}$	Gerard (1948)
Dog	ns	42/ns	2940 ppm-min (98 ppm x 30 min)	$L(CT)_{70}$	Postel and Swift (1945)
Dog	ns	6/ns	3000-5250 ppm-min (100-175 ppm x 30 min)	$L(CT)_{50}$	Patt et al. (1946)
Dog	Mongrel	15/M,F	3700 ppm-min (124 ppm x 30 min)	$L(CT)_{90}$	Schultz (1945)
Goat	ns	ns/ns	1650-3300 ppm-min (550 ppm x 3 min) (110 ppm x 30 min)	$L(CT)_{100}$	Winternitz et al. (1920)
Goat	ns	30/F 1/M	2500 ppm-min (250 ppm x 10 min)	$L(CT)_{50}$	Karel and Weston (1947)
Goat	ns	61/ns	2700 ppm-min (180 ppm x 15 min)	$L(CT)_{50}$	Underhill (1920)
Goat	ns	ns/ns	8750 ppm-min (8750 ppm x 1 min)	$L(CT)_{100}$ (all animals died within 4.5 hours)	Tobias (1945)
Ape	-	-	250 ppm-min (250 ppm x 1 min)	$L(CT)_{50}$	Chasis (1944)[b]
Ape	ns	ns/ns	330-600 ppm-min (110 ppm x 3 min) (20 ppm x 30 min)	$L(CT)_{100}$	Winternitz et al. (1920)
Ape	Rhesus monkey (*Macaca mulatta*)	19/M 18/F	500 ppm-min (500 ppm x 1 min)	$L(CT)_{50}$	Weston and Karel (1947)
Ape	-	-	1087 ppm-min (1087 ppm x 1 min)	$L(CT)_{100}$	Moor and Gates (1946)[b]
Ape	ns	ns/ns	2010 ppm-min (67 ppm x 30 min)	Mean survival time of 3.5 hours	Winternitz et al. (1920)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Repeated Exposures					
Mouse	ns	20/ns	300 ppm-min (1 ppm x 300 min) repeated daily for 5 days	$L(CT)_{90}$	Cameron and Foss (1941)
Rat	ns	10/ns	60 ppm-min (0.2 ppm x 300 min) repeated daily for 5 days	Lung edema in 20% of the animals	Cameron et al. (1942a)
Rat	ns	10/ns	300 ppm-min (1 ppm x 300 min) repeated daily for 5 days	Pulmonary edema in 80% of the animals	Cameron and Foss (1941)
Guinea pig	-	-	30 ppm-min (3 ppm x 10 min) repeated daily for 5 days	Bronchitis; bronchiolitis	Cordier and Cordier (1942)[b]
Guinea pig	ns	10/ns	60 ppm-min (0.2 ppm x 300 min) repeated daily for 5 days	Lung edema in 70% of the animals	Cameron et al. (1942a)
Guinea pig	ns	10/ns	300 ppm-min (1 ppm x 300 min) repeated daily for 5 days	Lung edema in 100% of the animals	Cameron and Foss (1941)
Rabbit	ns	10/ns	60 ppm-min (0.2 ppm x 300 min) repeated daily for 5 days	Alveolar edema in 50% of the animals	Cameron et al. (1942a)
Rabbit	ns	10/ns	300 ppm-min (1 ppm x 300 min) daily for 5 days	$L(CT)_{20}$	Cameron and Foss (1941)

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TABLE 4-1. (continued)

Species	Strain[a]	Number/ sex	Exposure (CT)	Effect	Reference
Cat	ns	6/ns	25-37.5 ppm-min (2.5-3.75 ppm x 10 min) repeated daily for up to 12 days	Isolated occurrences of alveolar edema and bronchiolitis	Cordier and Cordier (1953)
Cat	ns	2/ns	60 ppm-min (0.2 ppm x 300 min) repeated daily for 5 days	Lung edema in 50% of the animals	Cameron et al. (1942a)
Dog	Mongrel	14/ns	720-1200 ppm-min (24-40 ppm x 30 min) 1-3 times per week up to 12 weeks	Up to twentyfold increase in airway resistance with increasing exposure	Rossing (1964)
Goat	ns	2/ns	60 ppm-min (0.2 ppm x 300 min) repeated daily for 5 days	Slight hemoconcentration in one of two animals	Cameron et al. (1942a)
Goat	ns	2/ns	300 ppm-min (1 ppm x 300 min) reported daily for 5 days	Lung edema in both animals	Cameron and Foss (1941)

[a] no data available; ns, not specified.

[b] Based on data presented by Diller and Zante (1982).

TABLE 4-2. MEDIAN LETHAL INHALATION DOSE OF PHOSGENE FOR VARIOUS SPECIES (ppm-min)

Species	$L(CT)_{50}$
Cat	~ 200
Ape	~ 300
Rat	~ 400
Guinea pig	~ 500
Man	~ 500
Mouse	~ 500
Dog	~1000
Rabbit	~1500
Goat	~2000

Source: Diller and Zante (1982)

predicted by the CT = K equation (Figure 4-1). Although Flury's work supported the concept of Haber's Law, questions were raised by other investigators about its validity.

Bruner and Coman (1945) reviewed the available literature and concluded that "for practical purposes the CT product for a species may be regarded as a constant within the middle ranges of concentrations and duration of exposure." However, they also stated that at the extremes of concentration the relationship completely breaks down. From the available data it appears that the CT = K relationship for lethality is valid for phosgene concentrations between 1 and 200 ppm and for exposure times long enough to negate the effects of an animal holding its breath.

More recently, Atherley (1985) reviewed the uses and limitations of Haber's Law as an index of exposure. Atherley cautioned that confusion between the use of dose and exposure, and insufficient consideration of time as a factor call into question the validity of its usage for many substances. Whereas Haber's Law does not hold for some other noxious gases, it appears to apply, within limits, to toxic endpoints of phosgene exposure.

Rinehart and Hatch (1964) studied the responses of 118 Wistar rats exposed to phosgene concentrations ranging from 0.5 to 4 ppm over time periods ranging from 5 minutes to 8 hours. The exposures were varied to give CT products between 12 and 360 ppm-min. Response was expressed in terms of impaired pulmonary gas exchange capacity as measured by the decreased rate of uptake of carbon monoxide (Long and Hatch, 1961) and ether. The authors concluded that the product of phosgene concentration and exposure time (CT) appears to be a

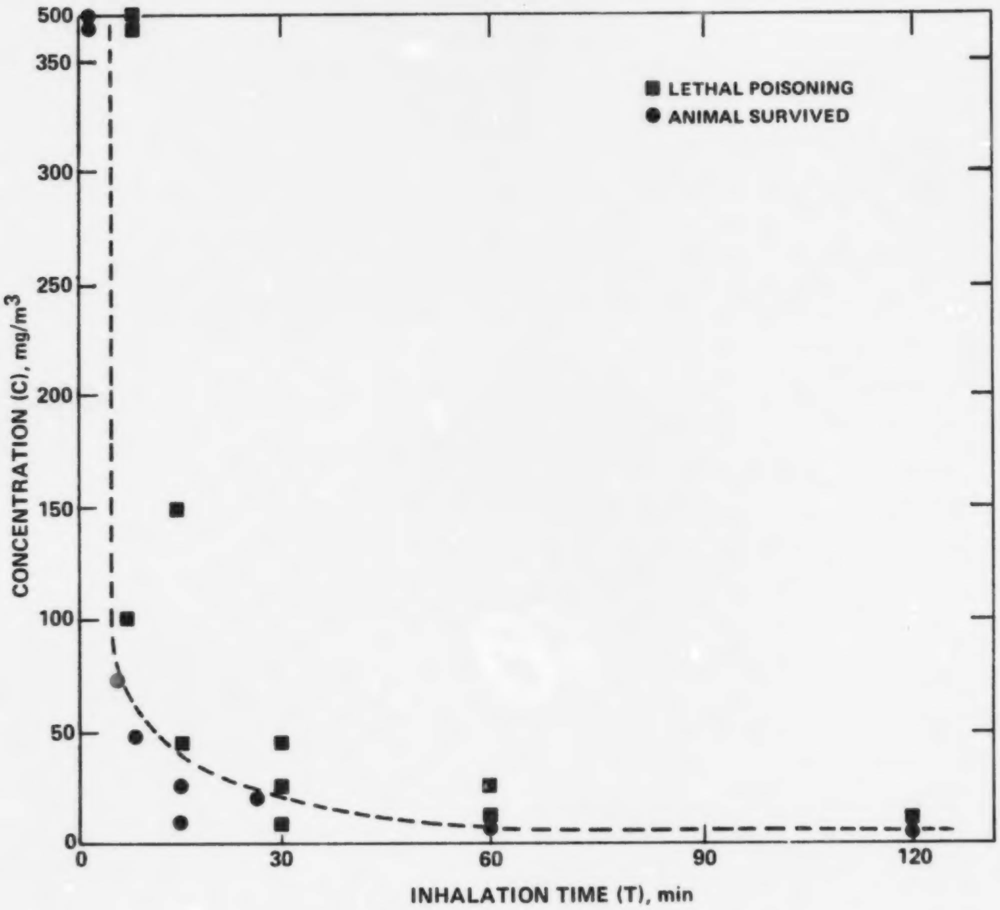

Figure 4-1. Exposure (C x T) of cats to phosgene.

Source: Adapted from Flury (1921).

suitable way to express the magnitude of phosgene dosage, since equal degrees of respiratory response were observed from exposures to various combinations of C and T that gave the same CT product.

4.1.2 Symptomatic Stages of Acute Phosgene Exposure

The lung appears to be the principal target organ for phosgene inhalation, and the characteristic pathologic feature is the delayed development of pulmonary edema. This was demonstrated in some of the earliest studies on phosgene poisoning carried out at the time of World War I. Underhill (1919, 1920), in his studies on the toxicity of phosgene, exposed over 500 dogs for 30 minutes to phosgene concentrations ranging from 44 to 120 ppm. He pointed out that phosgene acted chiefly as a respiratory irritant but was also a lacrimator. Very small doses (concentration not reported) scattered in the air caused coughing, watering of the eyes, and intense dyspnea. The influence of small doses was limited mainly to the terminal bronchioles and alveoli of the lungs. This effect produced edema of the lungs accompanied by an interference of pulmonary gas exchange and consequent cyanosis on exertion. It usually took several hours for the serious symptoms to develop. In the dogs exposed to high concentrations, there was slight lacrimation and uneasiness, and the pupils became clouded. Subsequently, the dogs developed a hard cough, respiration became more and more difficult (usually there was rattling in the throat), and death followed 3 to 12 hours after exposure. The heart action grew weaker as death approached, but persisted after all attempts at breathing had ceased. Changes in hematocrit were not prominent in the early stages of phosgene poisoning; however, as time passed, the blood assumed a sticky, concentrated consistency, probably reacting in time to impede heart action and to interfere with the proper blood supply to the tissues, and thereby altering metabolism.

Pointing out that pulmonary edema is a very prominent feature of phosgene poisoning, Underhill (1919, 1920) suggested that the edema may be an apparent attempt toward repair or alteration of injury. However, at sufficiently high exposure levels, the whole mechanism governing the exudation of tissue fluid was thrown out of control so that the response became overwhelming. Under these conditions, a reaction that initially may be regarded as beneficial eventually becomes a direct menace to continued existence by creating mechanical difficulties for respiration and circulation. Considering the changes in the blood and lungs at intervals following phosgene exposure, Underhill concluded that the development of edema is associated with well-defined changes in the fluid and electrolyte content of the blood and tissues, without an apparent increase in the permeability of the blood vessels. Fluid and electrolytes probably pass from the tissues to the blood in an attempt to compensate the latter for its loss as pulmonary edema fluid.

On the basis of alterations in hematocrit, Underhill (1919, 1920) conceived three stages in phosgene poisoning. In the first few hours (5-8) after phosgene poisoning, there was a slight, temporary dilution of the blood. Oxygen-carrying capacity, erythrocyte count, and total hemoglobin followed a curve parallel with that of changes in hematocrit throughout all stages of phosgene poisoning. In the second stage, the period of blood dilution was followed by an interval during which the hematocrit increased to a point far beyond the normal value and remained near this level for several hours. Edema reached its maximum development during this stage. After the period of increased hematocrit, the blood gradually became more dilute until it was slightly under the normal value, which was eventually regained and the animal recovered. Underhill ascribed the immediate cause of death in phosgene poisoning to blood concentration, with its attendant decrease in circulation, oxygen starvation of the tissues, fall in temperature, and, finally, suspension of vital activities.

Winternitz et al. (1920) carried out necropsy studies on the same dogs used by Underhill (1919, 1920). The changes found at necropsy after gassing varied greatly with the time the animals had survived; consequently, the animals were divided into three groups: animals dying or killed within 48 hours after gassing ("acute period"), those killed or dying after 3 to 10 days ("subacute period"), and those killed or dying after 11 to 129 days ("chronic period"). Gross findings on 260 dogs dying during the acute period showed frothy fluid oozing from the mouth, with some loss of weight, probably due to loss of fluid by mouth. There was engorgement of the great vessels in the abdomen and congestion of the viscera. The liver was enlarged and was a dark purplish color. The spleen was only slightly enlarged, but like the other abdominal organs, had the general appearance of acute congestion. The heart was generally enlarged, being more marked on the right than on the left side. The lungs were very voluminous and heavy. In animals dying in the first 12 hours, the edematous condition was not quite so marked, whereas in those dying between 24 and 48 hours it was often the most prominent feature, overshadowing the congestion and emphysema. Thus, in the first few hours before the edema became well developed, congestion was clearly responsible for the larger share of the increased pulmonary weight. Lung tissue increased rapidly in weight, reaching a maximum 18 to 24 hours after gassing when it often was, in fatal cases, more than four times the normal weight. The esophagus, stomach, intestines, pancreas, adrenals, thyroid, and brain showed no gross abnormalities. For 66 dogs dying in the subacute phase, infection of the respiratory tract was the main finding. If death was delayed more than four days, initial signs of repair, including organization of the exudate in the alveoli and bronchi, were generally seen. Congestion, edema, and emphysema were still present to a moderate degree. Edema was still marked, but less so than in animals in the acute group. The right side of the heart was still dilated in the subacute phase animals. The pathology of the 177 dogs dying after 11 to 129 days differed little from that observed in the animals which were killed or died in the subacute period. The healthier looking dogs in the third group, which were killed rather than dying spontaneously, showed moderately collapsed lungs. There was evidence of obliterative bronchiolitis and an associated atelectasis and emphysema. The presence of pathogenic organisms in many "recovered" animals was assumed to be an explanation for the fatal pneumonia that may develop even months after gassing.

The authors drew the following conclusions based on their studies. Phosgene inhalation in dogs found its chief anatomical expression in the respiratory tract. The lesions seen at autopsy varied according to the length of time the animal survived after gassing. At first there was severe pulmonary edema associated with extreme congestion, which reached a maximum toward the end of the first 24 hours and disappeared gradually in animals surviving 10 days or longer. The edema was associated with an inflammatory exudation of fibrin and leukocytes, which was most marked in and around the finer bronchioles and spread to a variable extent throughout the lung tissue. A typical lobular or pseudolobular pneumonia resulted. The character of the phosgene lesion was explained by the localization of the action of the gas upon the air tubes. The epithelium of the trachea and larger bronchi was not damaged, while that of the smaller bronchi and bronchioles was seriously injured, the more distal portion suffering most. In addition to the changes in the mucosa, the bronchi also showed pathological contractions and distortions, which resulted in more or less complete obliteration of their lumina. These, in turn, lead to mechanical disturbances in the air sacs, resulting in atelectasis or emphysema (Winternitz et al., 1920).

In a note on the comparative pathology of acute phosgene poisoning, Winternitz et al. (1920) concluded that the pathology of phosgene poisoning in the goat, dog, monkey, rabbit, guinea pig, rat, and mouse was similar. The important lesions were confined to the lower respiratory tract. These consisted essentially of an edema filling many of the alveoli, associated with inflammatory changes that began in the bronchioles and extended into the alveoli. There was a well-marked variation in species toward phosgene lethality, which found its chief expression in the pathological picture as a difference in the amount of edema. Although edema developed more rapidly in the more susceptible species, it did not attain the degree commonly found in those animals that survived the same dose for a longer interval. This not only emphasizes the time factor in its production, Winternitz stated, but also clearly indicates that edema itself is not the cause of death.

The studies of Underhill (1919, 1920) and Winternitz et al. (1920) were carried out at Yale University. Meek and Eyster (1920) carried out a concurrent study on the pathological physiology of acute phosgene poisoning in dogs at the University of Wisconsin, with results comparable to those of Underhill and Winternitz et al. The animals were subjected for 30 minutes to phosgene at a concentration of 80 to 100 ppm, a level sufficient to produce death within 24 hours in most instances. A well-marked succession of events ensued, finally resulting in typical pulmonary edema. In the first stage, prior to edema development, there was early injury to the linings of the deep respiratory passages. Irritation from this resulted in a certain amount of reflex cardiac inhibition and vasoconstriction. Coincident with these changes, there was a direct action of the gas on the red blood cells, which caused them to agglomerate and obstruct the pulmonary capillaries. This in turn put a strain on the right side of the heart, with a right-sided cardiac dilatation being apparent. Even during this stage, the injury to the alveolar membranes and the increased pressure initiated the transfusion of fluid from the blood into the tissue spaces and later into the air passages of the lungs. The rapid development of this edema was the major characteristic of the second stage. It resulted in hemoglobin concentration, reduction in blood volume, and decreases in heart size, all of which proceeded to extreme degrees. Death under such conditions was either due to the edematous condition of the lungs, interfering sufficiently with exchange so that the animal asphyxiated, or the blood volume was so reduced that even though the hemoglobin was oxygenated there was not enough fluid to secure its proper distribution to, and circulation in, the tissues. In either case, the tissues died of oxygen starvation. The authors concluded that death was due to a combination of the two causes.

4.1.3 Lung Tissue Analysis After Acute Phosgene Exposure

Cameron et al. (1942b) exposed a group of animals to phosgene at an average concentration of 3.47 mg/m^3 (0.86 ppm) for a single 5-hour exposure. The exposed animals consisted of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, 2 monkeys, and 2 goats. On the morning following exposure, 10 percent of the rats (1/10) and 60 percent of the mice (12/20) were dead. There were no other mortalities, although one cat and one monkey were very ill and exhibited labored breathing. All survivors of the experiment were killed on the morning following exposure. All animals were necropsied, and one lung from each animal was fixed in formalin for sectioning. Upon examination, 54 of 56 animals (96.4 percent) showed microscopic evidence of pulmonary involvement that was severe in 29 animals (39 percent), mild in 17 (31 percent), and slight in 16 (30 percent). The most frequent effect noted in the lungs was edema.

Cameron and Courtice (1946) studied the production and removal of edema fluid in lungs after exposing rabbits, dogs, and goats to 440 mg/m^3 (110 ppm) of phosgene. Edema fluid was collected by inverting the animal immediately after death or when the animal was killed. In 24 rabbits exposed to phosgene for 15 to 30 minutes, increased time of exposure caused edema of greater severity. Rabbits exposed for 30 minutes usually died quickly with massive pulmonary edema. Yet all groups, regardless of extent of edema, showed little or no hemoconcentration, indicating that withdrawal of fluid from undamaged tissues into the blood was also rapid. The edema fluid had the same protein concentration as the plasma, suggesting an increase in capillary permeability. In studies on 12 dogs and 2 goats exposed to phosgene for 10 to 30 minutes, considerable hemoconcentration occurred as fluid was lost into the lungs. As edema developed, lymphatic flow increased rapidly in dogs exposed to phosgene, reaching levels many times higher than normal. However, the lymphatics removed only about 10 percent of the pulmonary edema fluid formed, when death occurred from 6 to 12 hours after exposure. After 24 hours, the production of edema fluid seemed to lessen and the animal recovered. Nonetheless, for dogs killed several days later, when hemoconcentration had disappeared, the lungs were often still edematous. Based on these studies, the authors concluded that anoxia due to pulmonary edema was a more important factor in causing death than hemoconcentration and a decreased blood volume.

A systematic analysis of the sequence of tissue changes in lungs of animals following exposure to phosgene was carried out by Coman et al. (1947). The dogs, cats, rabbits, and guinea pigs employed in the studies were adults of mongrel origin; the rats were of the Wistar strain. The animals were exposed to potentially lethal doses of phosgene which varied according to species susceptibility. Exposure times varied from 3 to 30 minutes for dogs, from 3.5 to 57 minutes for rats, and were 13, 35, and 9 minutes for the cats, rabbits, and guinea pigs, respectively. The course of phosgene poisoning was divided into three phases: (1) the incipient phase, which extended from gassing up to two to six hours; (2) the critical phase in which the majority of deaths occurred (in survivors, this phase ended about three days after exposure); and (3) the regressive and reparative phase, which extended from the fourth day onward. Extensive emphysema was the earliest prominent lesion in animals exposed to potentially lethal doses of phosgene. Sloughing of the bronchiolar mucosa and questionable bronchial restriction were also found at once after gassing. Peribronchial edema, pulmonary congestion, and alveolar edema developed subsequently and in that order. The rapidity of development and extensiveness of these lesions were roughly proportional to the severity of the exposure. Recovery from the massively edematous lung was found to be primarily a process of resorption of edema fluid and scarring. A moderate cellular inflammatory reaction accompanied this process, sometimes so excessive as to resemble bronchopneumonia. The late effects of phosgene poisoning consisted of pulmonary scarring, lobular emphysema, and small, irregular areas of atelectasis and bronchitis. Apart from effects on lungs, dogs poisoned by doses of phosgene, which killed 70 to 99 percent of the group, immediately showed bradycardia, a general lassitude, motor activity of the colon and bladder, and a rapid, shallow type of restricted breathing. There was no relationship between the severity of these signs and survival. The authors concluded that there was no asymptomatic interval between exposure and onset of overt damage. Rather, the anatomic pulmonary damage, begun during gassing, steadily progressed. The results of Coman et al. (1947) parallel those of Winternitz et al. (1920).

4.1.4 Measurement of Pulmonary Function

Gibbon et al. (1948) investigated the possibility that elevated pulmonary pressures might be a factor in the pulmonary edema produced by phosgene. This was done by direct measurement of the pulmonary arterial pressure and by evaluation of the pulmonary pressure gradient in cats. In studies using 5 cats exposed to highly lethal doses of phosgene at concentrations of 0.29 mg/L (72 ppm) for time periods ranging from 8.5 to 13 minutes, no abnormal elevations of pressure were found in the pulmonary artery up to 30 hours after gassing. These results seem to make untenable the hypothesis that the pulmonary edema of phosgene poisoning is of purely hydrostatic origin.

Long and Hatch (1961) described a sensitive means for measuring early and minimal degrees of functional pulmonary impairment in rats following exposure to phosgene, based on a reduction in the rate of respiratory uptake of carbon monoxide (CO). At least 8 unanesthetized rats were exposed to each of the following concentration ranges of phosgene for 30 minutes: 0.5 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to 5 ppm. Postexposure tests on CO retention, oxygen consumption and breathing frequency were run at intervals from 1 to 72 hours after exposure. There was a progressive loss of capacity to absorb CO over the first six to eight hours after exposure, followed by a prolonged period of recovery. Moreover, there was a direct correlation between the systematic decrease in the magnitude of the effect and the lowering of the phosgene concentration. Measurable changes in CO uptake were found even with the lowest level of exposure, below 1 ppm, and in the absence of microscopic changes at necropsy.

In a study designed to determine the increase in permeability of the respiratory membrane of rabbits after exposure to phosgene, Boyd and Perry (1960) exposed 62 male rabbits to 0.27 mg/L (67 ppm) of phosgene for 30 minutes. The animals were then divided into two groups and anesthetized with urethane, either immediately or 16 hours after gassing. Fluid was collected from the respiratory tract at hourly intervals after anesthetization. In preliminary experiments, this exposure killed 80 to 100 percent of the rabbits. The response to phosgene during the first six or seven hours after exposure consisted of a mild edema of the trachea, bronchioles, and alveolar tissues. Also, there was some congestion, emphysema, and contraction of pulmonary capillaries. In 19 of 31 animals anesthetized 16 hours after gassing for fluid collection, the pulmonary edema had markedly increased, there was more emphysema and some hemorrhage, the pulmonary capillaries were less contracted, and there was less edema in the bronchioles and trachea. In the other 12 animals, there was a premortal gush of respiratory tract fluid (60 times normal) similar in composition to blood plasma, and pulmonary edema was maximal. The animals also displayed intense hemoconcentration. The authors concluded that the clinical course of phosgene poisoning is characterized by a latent period of several hours following exposure, during which many pathological changes occur.

Results comparable to those found in rabbits were also obtained in cats and dogs (Boyd and Perry, 1963). Fifty-seven cats and 12 dogs were exposed to an estimated LD_{50} of phosgene, the concentration of phosgene varying between 0.10 and 0.30 mg/L (25-75 ppm) for 30 minutes of exposure. During the hour or two before death, the volume output of respiratory tract fluid increased some thirtyfold in half the animals (cats, ~35 ml/kg/24 hr; dogs, ~15 ml/kg/24 hr), and its lipid and sodium chloride contents were similar to those of blood plasma. The ability of the animals to excrete such large volumes of respiratory tract fluid appeared to be due to a marked reserve capacity of the ciliary drainage mechanism, which was evidently not affected by the dose of phosgene given to these animals.

4.1.5 Site of Lung Injury Following Acute Phosgene Exposure

The first changes occurring in lungs of dogs after inhalation of phosgene for a short time were examined by Diller et al. (1969) utilizing comparative radiographic studies as well as light and electron microscopy. Forty-two dogs (30 beagles and 12 mongrels) were exposed to either 94.5 or 107.5 ppm phosgene for 10 minutes. Examinations were carried out at various intervals after exposure. The first changes were found in the alveolar wall 1.5 hours after inhalation, with the alveolar epithelium appearing intensely folded. The alveolar wall was edematous, and the alveoli contained a cell-free exudate. The peripheral parts of the lung were emphysematous. The edema increased during the first hours. After rupture of the alveolar walls, the exudate contained fibrin and cellular debris. A severe bronchiolitis with some necrosis developed six to eight hours after phosgene inhalation. Lymphostasis occurred in the peribronchial interstitium. Roentgenograms at four hours revealed only acute emphysema, and six hours after inhalation, a lung edema was recognizable. These results would appear to support the conclusions of Boyd and Perry (1963, 1960) regarding the time sequence of pathological changes induced by phosgene.

Rinehart and Hatch (1964) studied the responses of 118 Wistar rats to phosgene exposure. Exposure concentrations were between 0.5 and 4 ppm for intervals ranging from 5 minutes up to 8 hours (CT values ranged between 12 and 360 ppm-min). Beginning changes in pulmonary performance were noted following exposures to CT values as low as 30 ppm-min. Deaths occurred at doses greater than 180 ppm-min, with associated reduction in CO uptake to less than 50 percent of the normal value. Survival from exposures exceeding 300 ppm-min was less than 40 percent. Low-level exposures to phosgene, below 100 ppm-min, appeared mainly to affect the ventilatory process through increased resistance to breathing and poorer distribution of the ventilating air in the lungs. Above 100 ppm-min, loss of diffusing capacity became relatively important. The authors surmised that these differences in nature of response reflect differences in the major site of action, with the respiratory bronchioles being the site in the first case and the alveoli in the second.

In an extension of the studies of Rinehart and Hatch (1964) on the dependence of the site of lung injury on the level of phosgene administered, Gross et al. (1965) also exposed 117 male Wistar rats to phosgene at concentrations between 0.5 and 4 ppm for periods ranging from 5 minutes to 8 hours. The CT values ranged from 13 to 360 ppm-min. The animals were killed four days after phosgene exposure and the lungs examined. A second series of 15 rats was exposed to 1.7 ppm phosgene for 120 minutes and then killed in groups of 3 at 4, 8, 24, and 48 hours and 1 week after exposure. In addition, a third group of rats was exposed to 2.2 ppm phosgene for 80 minutes and killed 3 months after exposure. The authors found that at the doses administered, there was development of a chronic pneumonitis, with the severity of response depending on the dose level. At the lower concentrations, relatively small amounts of the alveolar surface epithelium, involving only adjacent alveoli, were affected. At higher concentrations, little unaffected alveolar tissue was present and the pneumonitis was considered severe. The authors attributed this difference to the two target sites involved, i.e., the alveolar surface epithelium and the alveolar capillary. A reversible chronic pneumonitis resulted when the phosgene dose was low and when the alveolar epithelium was merely irritated. In contrast, when high concentrations of phosgene were administered, much of the surface epithelium was destroyed, rendering it incapable of reacting to injury. The unprotected capillary was then severely injured and responded with the profuse exudation of pulmonary edema.

Gross et al. (1967) elaborated on their view regarding the nature of the response of respiratory tissue to irritants, pointing out that the alveolar wall is composed of two embryologically different tissues. The network of alveolar capillaries is of mesodermal origin, whereas the alveolar membrane is of entodermal origin. These two tissues respond differently to injury. A respiratory irritant in dosages sufficient to penetrate the alveolar membrane and injure the subjacent capillary will cause the classical reaction of all capillaries--namely, the loss of semipermeability and leakage of fluid or cells or both into the air spaces, resulting in pulmonary edema or pneumonia. If the dosage of the irritant is not sufficient to injure the capillaries, only the alveolar membrane may respond to the injury. This is characterized by a proliferation of cohesive, alveolar cells and the elaboration of an argyrophilic supporting stroma.

Hatch et al. (1986) investigated the concentration-response of inhaled phosgene in rabbits, guinea pigs, rats, hamsters, and mice. Lavage fluid protein accumulation 18 to 20 hr after 4 hr exposures to 0.1, 0.2, 0.5 and 1.0 ppm phosgene was used as the indicator of pulmonary edema. All species had similar basal levels of lavage fluid protein. Phosgene significantly affected mice, hamsters, and rats at 0.2 ppm and above, while guinea pigs and rabbits were significantly affected only at 0.5 ppm and above. No significant effects were observed at the 0.1 ppm exposure level.

Diller et al. (1985) carried out studies on 155 male albino Wistar rats to establish the minimal inhalation doses of phosgene necessary for the production of changes within the lung blood-air barrier. Groups of 10 to 15 animals were exposed to a total dose of 50 ppm-min of phosgene at 5, 2.5, 1, 0.15, or 0.1 ppm for 10, 20, 50, 300, or 500 minutes, respectively. The animals were sacrificed 48 hours after exposure for either morphological examination by light and electron microscopy alone, or in combination with bronchoalveolar lavage. Another group of 14 rats was exposed to 0.1 ppm x 250 minutes (CT = 25 ppm-min) phosgene and sacrificed at 48 hours, and a final group was exposed to 0.1 ppm for 60 minutes. The authors found that at least 50 ppm-min (5 ppm x 10 minutes) was necessary for the production of alveolar edema, the minimal effective concentration of phosgene being 5 ppm. The smallest phosgene exposure to produce an increase in pulmonary lavage protein content was also 50 ppm-min, and the smallest phosgene exposure to produce widening of pulmonary interstices was 25 ppm-min. There was no phosgene threshold concentration for these latter two parameters, which was assumed to be indicative of physiological compensatory mechanisms within the blood-air barrier. The authors concluded that the primary localization of pulmonary damage by phosgene depends on the concentration of gas used. At very low concentrations of phosgene (0.1-2.5 ppm), the changes are primarily located at the transition from terminal bronchioles to alveolar ducts; at higher concentrations of phosgene (5 ppm), it is primarily the alveolar region that exhibits alterations (Type I pneumocytes) associated with the initiation of edema. The authors suggested that these results would appear to confirm a concentration dependence of the primary localization of phosgene damage, as had been suggested earlier by Gross et al. (1965).

4.1.6 Blood Circulation Disturbances After Acute Phosgene Exposure

Although the characteristic pathologic feature of phosgene poisoning is pulmonary edema, disturbances in blood circulation are also evident (Underhill, 1919, 1920). Hemodynamics in phosgene poisoning and the possible mechanisms contributing to circulatory disturbance were investigated by Patt et al. (1946). Circulatory measurements were made on both anesthetized and unanesthetized dogs before and after exposure to phosgene at concentrations of 0.4 to 0.7 mg/L (100-175 ppm) for 30 minutes. Circulatory changes were followed at various intervals for 13 hours after gassing. Heart rate fell precipitously with gassing, then slowly rose to above the initial value. Arterial pressure fell distinctly and progressively with time after gassing. The fall in arterial pressure was sharper in the short-survival groups. Venous pressure did not change significantly or consistently. Pulmonary circulation time was increased on the average by two-thirds at 8 to 12 hours after gassing, often accompanied by a rising arteriovenous oxygen difference in the systemic circuit. The hematocrit rose sharply in relation to the increase in circulation time with a concomitant increase in blood viscosity. The authors concluded that the circulatory disturbances observed may contribute to the final physiologic breakdown by exaggerating the tissue anoxia already present because of the low arterial oxygen saturation. They believed, however, that death is due primarily to an interference with oxygen uptake through edematous lungs. If the animal survives the acute stage of pulmonary edema with its attendant anoxia, circulatory failure may become a more important factor in the ultimate outcome.

4.1.7 Recovery After the Development of Acute Symptoms

Koontz (1925) attempted to determine whether pathologic lesions persist in the lungs of dogs that have been gassed with phosgene but have recovered from all symptoms. Dogs of an unspecified breed were gassed with the minimum lethal dose (concentration not reported) of phosgene. Ninety-five dogs that recovered from the gassing, as determined after temperature, pulse, and respiration became normal, and all symptoms such as coughing, depression, and general lack of well-being had disappeared, were studied. Of these, 34 died or were killed in the kennels by other dogs, and the other 61 were sacrificed at intervals ranging from 2 weeks to 15 months after recovery. The lungs of 68 of the dogs appeared normal by gross examination. Of the remaining 27, 3 showed emphysema and 2 showed pneumonia. The others had lesions such as congestion, hemorrhage, edema, and emphysema in varying degrees of intensity. Most of these gross lesions were found in dogs that died. Microscopically, of the 95 dogs studied, the lungs were normal in 21 and almost normal in another 24, showing only small areas in which there were lesions of minor degree. Lesions in the lungs of other dogs consisted primarily of bronchi plugged with cellular debris, and atelectasis in adjacent lung tissue in the early stages of recovery, progressing to obliterative bronchiolitis and patches of organization. The lungs took on a more normal appearance as the time from date of recovery increased.

Durlacher and Bunting (1947) exposed 31 dogs of both sexes (breed not specified) to phosgene at 0.29 mg/L (72 ppm) for 30 minutes. The animals were then divided into several groups and given a variety of treatments, including 60 percent oxygen therapy during the pulmonary edema phase. Consolidation of one or more lobes of the lung was found in the animals four to nine days after phosgene exposure. Organization of the pulmonary exudate occurred as the initial edema subsided, resulting in severe late anoxemia and mortality in spite of oxygen therapy during this period. Two dogs that survived the stage of pulmonary organization showed only focal scars in the pulmonary parenchyma and bronchioles 27 and 59 days after gassing.

4.2 HUMAN STUDIES

4.2.1 Odor Detection Threshold of Phosgene

The National Institute of Occupational Safety and Health (1976) reported the results of two studies that investigated the odor detection threshold for phosgene. In one report, 56 "technically trained" military personnel were exposed to increasing concentrations of phosgene until all the subjects could detect the gas by odor. The lowest concentration that could be detected by some of the subjects was 0.4 ppm. At concentrations of 1.2 and 1.5 ppm, 39 and 50 percent of the subjects reported detecting phosgene, respectively. In the second study, a group of four volunteers were asked to identify the lowest concentration at which they all could recognize the distinctive "hay-like" odor of phosgene. The authors of this second study distinguished this value, 1.0 ppm, from the "detection threshold," described above which they felt was neither reliable nor reproducible.

4.2.2 Acute Pathology

Within certain limits, the acute toxicity of phosgene to humans is dependent upon the concentration of the gas and the length of time that an individual is exposed. An extensive review of the literature on the health effects of phosgene (both animal and human) led Diller and Zante (1982) to construct a table to describe the concentration-effect relationships of phosgene exposure in humans (Table 4-3).

TABLE 4-3. CONCENTRATION-EFFECT RELATIONSHIPS OF PHOSGENE EXPOSURE

Perception of odor	>0.4 ppm
Recognition of odor	>1.5 ppm
Signs of irritation in eyes, nose, throat, and bronchi	>3 ppm
Beginning lung damage	>30 ppm-min
Clinical pulmonary edema	>150 ppm-min
$L(CT)_1$	~300 ppm-min
$L(CT)_{50}$	~500 ppm-min
$L(CT)_{100}$	~1300 ppm-min

Source: Diller and Zante (1982).

At very high levels (>200 ppm), phosgene crosses the blood-air barrier, reaches the pulmonary capillaries, and reacts with blood constituents (Diller, 1985a). Death occurs rapidly from acute overdistension of the right heart, "acute cor pulmonale." The pathology associated with this severe poisoning includes hemolysis in the pulmonary capillaries with hematin formation, congestion by erythrocyte fragments, and stoppage of capillary circulation. Death due to such massive exposure is relatively rare. More commonly, individuals are exposed to small or moderate quantities of phosgene; the pathology resulting from these lower exposures is quite different than that described above.

The pathogenesis following acute exposure to small or moderate concentrations of phosgene (about 30-300 ppm-min) shows three distinct phases: initial reflex syndrome, clinical latent phase, and clinical edema phase (Diller, 1985a). Immediately after exposure, the victim usually feels an irritation of the eyes and throat and pain or tightness in the chest. He may also complain of shortness of breath on exertion, an irritating cough, and nausea and vomiting. These initial symptoms abate rapidly and are followed by the clinical latent phase, which is relatively free of symptomatology. A few patients return to work during this period of subjective well-being. The duration of the latent phase is inversely proportional to the inhaled dose: after relatively large doses, it may be 1 to 4 hours and after small doses, 8 to 24 hours (Diller, 1985a).

The latent period ends when the amount of edema fluid in the lungs becomes sufficient to interfere with respiration. At the onset of the clinical edema phase, the patient experiences a definite shortness of breath. He also presents a productive cough, expectorating large amounts of frothy, often bloody, sputum. The mucous membrane of the bronchi becomes necrotic and is shed. Leukocytes migrate into the bronchiole walls and into the alveolar interstices. The patient becomes anoxic and cyanotic. If the patient is not treated properly, death usually occurs as a result of paralysis of the respiratory center due to anoxemia. Even with effective treatment of the anoxemia, death may result from circulatory shock. In the absence of adequate antibiotic therapy, death may occur from superinfectious pneumonia because of increased susceptibility to infection.

Ardran (1964) reported that the development of pulmonary edema in both humans and dogs after exposure to phosgene could be predicted by viewing radiographs taken on inspiration and expiration. If the film taken on expiration shows an increase in lung volume, this is an indication that edema may develop. The lung volume returns to normal as the edema resolves. The author stated that these changes can be observed within minutes of exposure and that, in 20 years of using this technique in both clinical and experimental situations, it has been a reliable indicator. However, this technique of predicting the onset of pulmonary edema by evaluating an initial overdistension of the lungs is in contrast to the findings of Diller (1976).

4.2.3 Case Studies of Direct Phosgene Exposure

The following case studies expand on the generalities mentioned above and also present the diverse ways in which phosgene intoxication may be encountered. Delépine (1922) presented a detailed description of the symptomatology he experienced after acute exposure to phosgene. While conducting experiments on phosgene in 1917, the author was required to enter a room containing the gas (concentration not reported) at "frequent intervals over the course of three-quarters of an hour." He first noticed some mild irritation of his eyes and throat that was not severe enough to cause him to stop his experiments. At one point, however, the gas escaped the room and he was forced to breathe it freely. This brought about a violent fit of coughing. Delépine ran away, but during his flight he was required to stop frequently because of the violence of his cough. The cough lasted for about 15 to 20 minutes after he had left the building. He felt weak and dazed, and the open air seemed to smell of phosgene. His condition improved for the next three to four hours (clinical latency period); then he began to experience a choking sensation, giving him the sensation of impending death from lack of air. Recovery of normal breathing took several days, but a marked lassitude continued for an additional few days. No mention of any late sequelae of the poisoning was made; recovery seemed complete.

Two case histories of men exposed to phosgene gas were reported by Stavrakis (1971). In the first case, a 30-year-old male was accidentally exposed to an unknown quantity of phosgene while at work. The only reported initial effect was a short-lived cough. The patient finished his shift and went home. An hour later (4 hours postexposure) the cough recurred, this time accompanied by expectoration of some mucus. A short time later, he arrived at the hospital in serious condition with evidence of severe dyspnea, restlessness, chest pain, and a persistent, productive cough. A roentgenogram of the lungs showed the presence of pulmonary edema. The patient improved rapidly and was discharged from the hospital on the fifth day, free of symptoms. The condition of the patient after discharge was not followed up.

In the second case, a male, age 31, was exposed to phosgene when a pipe conducting the gas accidentally ruptured. That evening, he reported to the hospital with signs of acute progressive pulmonary edema and extreme hemoconcentration and leukocytosis. Despite aggressive therapy, the patient died 3.5 hours after admission.

Everett and Overholt (1968) described a case report of a 40-year-old male who received a "massive" exposure to phosgene. His medical history showed that he had been a cigarette smoker for many years, but had quit about a year before the accident and was in excellent health at that time. The initial effects of the exposure consisted of a cough, severe burning of the eyes, and an inability to "get his breath." These initial symptoms abated within two to five minutes, and the patient felt fine for the next two hours. A mild, hacking cough began two hours after exposure, and at three hours, mild dyspnea began. Six hours after exposure, he was severely dyspneic and moist rales were noted throughout both lung fields. The patient was admitted to intensive care about eight hours postexposure. He was anxious, agitated, cyanotic, complained of thirst, and had a constant cough that yielded copious amounts of yellow-brown, watery, frothy sputum. A roentgenogram disclosed severe pulmonary edema. Pulmonary function studies revealed acute emphysema. CO diffusion capacity was normal, and the patient was not hypotensive at any time. By the fifth day in the hospital, the patient was asymptomatic; and by the seventh hospital day, studies of pulmonary function showed no abnormalities and a chest X-ray was normal. His health was followed up for two years after the accident; no abnormalities were reported.

Case studies of two victims of phosgene inhalation were reported by Regan (1985). On December 9, 1977, a major phosgene emission occurred in a toluene diisocyanate production unit. One man, age 31, was admitted to the hospital eight hours later with clinically apparent pulmonary edema. He had rales in both lungs and left chest pain. His arterial blood gases were normal. The patient recovered quickly and returned to work six days after the accident. His followup (time not specified) was completely normal.

A second man, age 47, was admitted to the hospital 11 hours after the phosgene emission. He was dyspneic, had bilateral rales, and an X-ray indicated pulmonary edema. During treatment, the patient's condition deteriorated, with worsening blood gases ($PaO_2 = 60$). With intubation, the patient produced a large amount of pulmonary edema fluid. The patient remained in critical condition for the next three days. Clinical signs included low right-side heart pressure, low arterial pressure, hemoconcentration, and leukocytosis. Twelve days after the accident, the patient was completely asymptomatic. A pulmonary function study performed about four weeks after the accident revealed a mild degree of pulmonary obstruction that the author attributed to the patient's smoking.

The following case report (Bradley and Unger, 1982) illustrates that effective therapy that is sufficient to prevent death due to anoxemia in cases of severe phosgene poisoning may not prevent a later death from circulatory shock. The patient was a 23-year-old male, a nonsmoker who had been in good health. He was exposed to the concentrated gas for five to ten seconds, which produced an immediate cough, but no nausea or vomiting. Approximately one-half hour later, he experienced secondary symptoms such as dyspnea and tightness in the chest. By the time the patient reached the hospital, he was cyanotic, hypotensive, and had a rapid heartbeat and rapid, shallow breathing. A chest roentgenogram showed pulmonary edema. Four hours after exposure, he was intubated because of progressive respiratory distress and hypoxia. More than 300 mL of blood-tinged, frothy fluid were suctioned initially, and copious secretions were suctioned for the next 24 hours.

The patient was transferred to intensive care, and a complete laboratory workup was done. Pertinent findings included severe pulmonary edema (without cardiomegaly), leukocytosis, hemoconcentration, and abnormal coagulation values, indicating disseminated intravascular coagulation. Protein content of the pulmonary edema fluid was also high (4.8 g/dL). Aggressive therapy, including mechanically assisted breathing, was used to combat the hypoxia, but the patient developed ventricular fibrillation and died after six days in the hospital. No autopsy was performed.

Of historical significance is an accident that occurred in Hamburg, Germany, in 1928. On May 20 of that year, 11 metric tons (24,640 pounds) of "pure phosgene" escaped from a storage tank. The weather was warm and dry and there was a light northeasterly wind. Within a few hours after the leak began, people started reporting to area hospitals, some having been affected by the phosgene gas as far as six miles from the site of release. A total of 300 people reported ill within a few days, including 5 firemen and 8 security officers who were attempting to rescue affected civilians. One particular hospital admitted 195 victims on the evening of May 20. Of those, 17 were very ill, 15 were moderately ill, and the rest were only slightly affected. The history of the disaster as well as case reports of seven of the ten people who died as a result were reported by Hegler (1928).

With few exceptions, the symptomatology exhibited by the victims of the Hamburg disaster was identical to that reported above for victims of accidental workplace exposures to phosgene. One exception was a 52-year-old Hamburg man who died 11.5 days after exposure. At the time of the accident he was sitting in a park near the phosgene release area. His initial symptoms were typical and included headache, dizziness, nausea and vomiting, an irritant cough, and a sickening-sweet taste in his mouth. These initial symptoms abated and he felt better until a marked feeling of tightness in his chest began. He reported to the hospital 11 hours after exposure showing signs of pulmonary edema. He was cyanotic, had a very difficult time breathing, and rales could be heard throughout his lungs. He also exhibited other symptoms common to phosgene poisoning including pain in his chest, elevated pulse rate and temperature, and an irritant cough that produced blood-tinged, frothy sputum. On the following day he felt a little better, but was still dyspneic and showed unusual signs of brain dysfunction including an intermittent dimming of consciousness, or confusion as occurs with delirium tremens. Seven days after exposure, the patient developed a clot in his left calf, which cut off circulation to the limb, and eventually lead to gangrene. His lungs were clearer and he produced less sputum. The dyspnea was still present, but was greatly diminished by a medicine used to treat asthma. He died 11.5 days after his exposure to phosgene, apparently from a blood clot lodged in his lung (Hegler, 1928).

Autopsies on six of the fatalities of the Hamburg accident, including the one described above, were performed by Wohlwill (1928). In general, abnormalities were found only in the lung. Fatty degeneration of the kidneys, liver, and heart that was present in a few cases was felt to be secondary to the pulmonary lesions. However, in the case described above, there were additional processes noted in the gray matter of the brain and spinal cord as well as hyperemia and signs of bleeding in the white matter of the brain. Wohlwill suggested that the cause of these lesions of the brain was of a chemical nature, and not due solely to anoxia or reduced circulation. However, he also stated that all of the extrapulmonary abnormalities observed were secondary to pulmonary damage.

A third report on the Hamburg disaster was published by Mayer (1928). This report discussed hematological findings on several victims of the disaster, but does not add significantly to an understanding of the consequences of such a disaster.

The only reference to the prognosis of the exposed victims was a statement by Hegler that there were no late damages two months after the accident. Followup studies to determine the long-term health effects of phosgene exposure on the survivors were not reported. Also, other adverse effects of phosgene exposure were not reported. No other reports in the scientific literature regarding the Hamburg disaster were found.

Numerous other case studies of phosgene poisoning have been reported that support the symptomatology presented above (e.g., Mahlich et al., 1974; Cordasco and Stone, 1973; Steel, 1942).

4.2.4 Indirect Phosgene Exposure

Numerous incidences of phosgene poisoning have been reported where the victim was working with substances other than phosgene.

4.2.4.1 Butyl Chloroformate Exposure. Fabre et al. (1983) reported an incident where a man, age 48, was exposed to butyl chloroformate (phosgene + butyl alcohol) when a canister containing the liquid exploded. The explosion splashed the liquid into his eyes and face, producing a complete blindness that lasted about 15 minutes and burning sensations on his face and lips. The patient arrived at the hospital an hour after the accident, presenting signs of bronchial and facial irritation. Pulmonary and cardiovascular examinations showed no serious problems at that time. However, a roentgenogram taken the following day showed signs of pulmonary edema and the patient was also hypoxic. Symptomatic treatment was initiated, and by the seventh day after the accident the hypoxia had regressed and a chest X-ray was normal. The patient was reexamined 12 days later and all findings were normal.

4.2.4.2 Carbon Tetrachloride Exposure. One case has been reported in the literature of probable phosgene toxicity through the use of a carbon tetrachloride fire extinguisher (Seidelin, 1961). A 16-year-old woman was admitted to the hospital about ten hours after attempting to put out a fire with a carbon tetrachloride (CCl_4) fire extinguisher. She apparently had not been exposed to great heat, but had inhaled smoke and fumes that made her cough at the time. She felt well for the next six hours and then began to experience a cough and some difficulty in breathing. When seen at the hospital, her condition had worsened; she had a persistent, unproductive cough, was extremely breathless, and was deeply cyanosed. She also presented a rapid heartbeat and rate of breathing, and a moderate leukocytosis. Her blood pressure and temperature were normal. A chest examination disclosed indications of acute emphysema, and a roentgenogram revealed severe bilateral pulmonary edema. She was placed immediately on oxygen therapy, but continued to worsen, losing consciousness and remaining cyanosed. She began to improve eight hours later with expectoration of small quantities of frothy, very slightly blood-stained sputum. Her condition was greatly improved the next day, though her cough persisted and she required oxygen therapy to prevent anoxemia. She was discharged from the hospital on the 13th day, apparently fully recovered. When last seen six months later, her perfect health had continued and her chest radiograph was normal. The author indicated that this patient had suffered from phosgene poisoning because her clinical signs matched those of people exposed to phosgene gas and because CCl_4 decomposes to phosgene when in contact with hot surfaces (Yant et al., 1936).

4.2.4.3 Methylene Chloride Exposure. Gerritsen and Buschmann (1960) reported two cases of phosgene poisoning caused by the use of chemical paint removers containing methylene chloride in poorly ventilated rooms heated by kerosene stoves. In the first case, a 52-year-old painter used a chemical paint remover in the presence of a kerosene stove for several hours, noticing only a burning sensation in his throat. At lunch, the painter became aware of a feeling of tightness in his chest and visited his physician, who made an incorrect diagnosis of influenzal bronchiolitis. The patient later returned to his physician and was found to be dyspneic and cyanotic. He was sent to the hospital, but died despite efforts to save him. An autopsy revealed extensive degenerative changes in the epithelium of the trachea, bronchi, and bronchioli together with hemorrhagic edematous focal pneumonia.

By attempting to simulate the exact conditions that the painter was exposed to, the authors calculated that the atmosphere the patient breathed could have contained as much as 16 ppm phosgene after only 3 minutes and may have reached a maximum of 128 ppm after 12 minutes. The particular chemical paint remover used by the painter contained 92 percent volatile solvent consisting almost entirely of methylene chloride with small amounts of ethanol and trichloroethylene.

The second case reported by Gerritsen and Buschmann is noteworthy because it involved a 38-year-old woman in her seventh month of pregnancy. She worked for about three hours in a closed cellar using a chemical paint remover (containing methylene chloride) in the presence of a kerosene stove. Some hours later she felt some tightness in her chest and expectorated some blood-stained sputum. She went to her physician, who also misdiagnosed the problem. The next morning she felt much worse, was dyspneic, and cyanotic. A chest X-ray indicated pulmonary edema. Recovery was fairly rapid, and two months later she gave birth to a healthy child. Another case of probable phosgene poisoning because of the breakdown of methylene chloride in a chemical paint remover was reported by English (1964).

4.2.4.4 Trichloroethylene Exposure. Several reports also indicate probable phosgene poisoning due to the breakdown of trichloroethylene (Glass, 1972; Glass et al., 1971; Nicholson, 1964; Spolyar et al., 1951; Derrick and Johnson, 1943). Only one representative case study will be detailed. Glass et al. (1971) reported an example of probable phosgene poisoning that occurred when a welder began welding metal studs that were soaked with trichloroethylene. The welder, age 45, had been a pack-a-day smoker since the age of 16, and had developed chronic bronchitis before this incident. He welded the wet studs all morning, and by 12:30 p.m., he experienced tightness in his chest and some difficulty in breathing. He generally did not feel well, and deep inspiration caused him to cough violently. That afternoon he welded only dry studs and felt much better. He woke up late the next morning after a comfortable night's sleep, again feeling tightness in his chest and some difficulty in breathing. On his way to work, he experienced a general lassitude and shortness of breath on exertion. He was seen by a doctor that morning and was diagnosed as having acute bronchitis induced by phosgene poisoning and chronic emphysema from his smoking. A chest roentgenogram showed the lungs to be clear throughout. A reexamination performed 3.5 months later showed the continued presence of pulmonary emphysema.

4.2.5 Late Sequelae of Acute Phosgene Poisoning

Diller (1985b) reviewed the literature on the late sequelae after phosgene poisoning. The weight of the evidence suggests that the vast majority of phosgene intoxications have a good prognosis. However, most of the victims of heavy acute poisonings complain of chronic symptoms such as shortness of breath on exertion or reduced physical fitness for several months to several years after the accident. While simple spirometry findings are usually normal, sophisticated pulmonary function studies often reveal abnormalities that may also require years to resolve. The length and severity of these chronic effects appear to be a function of smoking habits, previous pulmonary abnormalities, and psychological disorders, rather than the severity of the exposure. Preexisting chronic bronchitis may undergo severe and progressive deterioration after toxic pulmonary edema due to phosgene poisoning (Diller, 1985b). However, the historical data also indicate that acute exposure to phosgene neither activates preexisting, quiescent tuberculosis nor increases susceptibility to tuberculosis (Sandall, 1922; Berghoff, 1919).

4.2.5.1 Studies of World War I Gassing Victims. Thousands of cases of acute exposure to phosgene occurred during World War I, yet there are only limited data on the long-term effects on the victims. Berghoff (1919) examined 186

American soldiers who had been gassed with phosgene, but made only three conclusions regarding the long-term effects: (1) These men showed no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of healed or quiescent pulmonary lesions; (2) they presented little evidence of material destruction of lung tissue; and (3) victims diagnosed as having emphysema had a more protracted convalescence than those diagnosed as having bronchitis.

Sandall (1922) investigated 83 men who were awarded pensions by the British Army for war gas injuries. The gas that these men were exposed to was not specified, but exposure to phosgene was implied. The most common complaints three years after exposure were shortness of breath on exertion (70 percent of the men); cough and expectoration (54 percent); pain, or a feeling of tightness across the chest (25 percent); palpitation and occasional giddiness (14 percent); and nausea (12 percent). Seven percent of the men reported symptoms of neurasthenia. There were no positive cases of tuberculosis. In 53 percent of the men, no physical abnormalities of the lungs were noted.

4.2.5.2 Studies of Workplace Exposure. A followup pulmonary function study on ten men was performed by Diller et al. (1979) three to nine years after they had experienced acute phosgene poisoning in the workplace. The severity of intoxication ranged from "severest pulmonary edema" to slight respiratory effects (Table 4-4). The men had missed from 2 to 290 days of work due to the exposure. The reexamination included spirometry, total body plethysmography, blood-gas analysis at rest and during exercise, argon washout curves, helium mixing time, and CO diffusion rate. Special attention was paid to the smoking habits of the men. All ten patients stated that they had experienced aftereffects of the intoxications for one to three years postexposure. These chronic sequelae included shortness of breath on exertion, palpitation, feelings of pain or tightness in the chest, and increased perspiration, cough, and expectoration. At the time of reexamination, one of the five men who had developed pulmonary edema (case 1) had developed emphysema with obstruction and impaired CO diffusion rate. Of the five men with only minor phosgene intoxications, one also developed emphysema (case 10). The other men had normal spirometric values, though some abnormalities were found for some of the more sophisticated pulmonary function parameters. Stepwise multiple regression analyses of the whole group (n = 10) showed that the extent of pulmonary function impairment appears to be more dependent on smoking habits than on the severity or the elapsed time from the original intoxication.

TABLE 4-4. SEVERITY OF POISONING IN TEN MEN OCCUPATIONALLY EXPOSED TO PHOSGENE

Case	Age[a]	Smoking habits[b]	No. of Years after exposure	Clinical diagnosis	Days missed from work
1	40	++	3	Severest pulmonary edema	290
2	32	(0)	9	Severe pulmonary edema	30
3	37	++	3	Marked pulmonary edema	14
4	35	0	6	Moderate pulmonary edema	21
5	39	0	3	Slight pulmonary edema	14
6	44	(0)	3	Bronchitis	17
7	43	(+)	3	Bronchitis	3
8	41	(0)	3	Dyspnea without rales	3
9	28	++	3	Slight interference of respiratory gas exchange	2
10	39	+	3	Slight effects	2

[a] Patients' ages at the time of examination.

[b] Nonsmoker, 0; ex-smoker >5 years, (0); ex-smoker <5 years, (+); <10 cigarettes per day, +; 10-20 cigarettes per day, ++; rankings reflect smoking habits at the time of evaluation.

Source: Adapted from Diller et al. (1979).

Diller et al. (1979) also followed the case history of a man for 25 years after phosgene intoxication. The subject was a light smoker who had suffered from mild chronic bronchitis since childhood. At the age of 35, he was exposed to phosgene and developed severe pulmonary edema. He was hospitalized for seven weeks. During the following months, a reduction in general physical fitness and a deterioration of his bronchitis were observed. After two years, vital capacity (VC) and forced expiratory volume (FEV) measurements were reduced to 70 percent of the normal range. Ten years postgassing, frank pulmonary emphysema was diagnosed, with VC and FEV about 50 percent of the normal range. The subject had to take a premature retirement at the age of 52, 17 years after phosgene exposure. This case history illustrates that severe phosgene intoxication can produce a chronic deterioration of a preexisting pulmonary lesion (Diller, 1985b).

The late effects of phosgene poisoning in six workers who had suffered symptoms of acute exposure were discussed by Galdston et al. (1947). Special attention was paid to psychiatric evaluations and pulmonary function studies.

The latter included comprehensive ventilatory function tests and respiratory function tests. The results of these tests are presented in Table 4-5.

Case 1: A female, age 38, was accidentally sprayed in the face with liquid phosgene. Within a few hours she developed signs of bilateral pulmonary edema and acute emphysema. By day 12 after the accident, physical and X-ray examinations indicated that the lungs had returned to normal. When she was reexamined 14 months after the accident, ventilatory and respiratory function of the lungs were normal. However, a relative decrease in vital capacity and a relative increase in residual air were found, suggestive of early pulmonary emphysema. Nineteen months after the accident, she was still unable to return to work, complaining of tiredness, weakness, marked breathing difficulty on exertion and palpitations, sensations of a tight band around the lower part of the chest, weakness of the left side of the body with pain on exertion, nervousness when among people, and nightmares.

Case 2: A 39-year-old woman accidentally inhaled phosgene. There were no immediate disabling symptoms, and the patient worked the remainder of the shift. However, 41 hours after exposure she was admitted to the hospital and diagnosed as having severe pulmonary edema, acute emphysema, partial collapse of the left lower lobe, marked anoxemia, fever, and leukocytosis. The patient was discharged from the hospital 11 days after admission, experiencing only slight shortness of breath and no undue fatigue after moderately severe exercise. She returned to work one month after discharge. Exertional dyspnea was no longer a problem at that time.

When examined six months after the accident, pulmonary function studies indicated slight abnormalities in ventilatory and respiratory functions. When last seen 17 months after the inhalation of phosgene, the patient was working, had no complaints, and did not exhibit any abnormalities on physical examination.

Case 3: A male, age 30, took at least two full breaths of phosgene while filling shells with phosgene. He promptly experienced marked tightness in the chest, became nauseated, and vomited. After oxygen therapy, he returned to work and completed his shift. During the night, he experienced increasing respiratory distress, tightness in the chest, cough with expectoration of thick yellow sputum, and dizziness. He was admitted to the hospital the next day and was diagnosed as having pulmonary edema, acute emphysema, and marked anoxemia. The patient recovered quickly, was discharged from the hospital on day 13, and

TABLE 4-5. SUMMARY OF CLINICAL FINDINGS IN SIX WORKERS AFTER ACUTE OCCUPATIONAL EXPOSURES TO PHOSGENE

Clinical Parameter	Case Number[a]					
	1	2	3	4	5	6
Age	38	39	30	48	43	49
Sex	F	F	M	M	F	F
Months after accident[b]	14	6	6	3	5	5
Months worked with phosgene	6	12	18	24	2	1
Chronic symptoms	A	N	N	A	A	A
Physical signs						
Acute	A	A	A	A	N	N
Chronic	N	N	N	B	N	N
Roentgenogram of chest	N	N	N	N	N	N
Lung volume						
(Vital capacity + % residual air) =	N	N	N	A	N	N
Total capacity	B	N	N	B	N	N
Intrapulmonary mixing of gases	N	N	B	A	N	B
Pulmonary emptying	N	N	N	A	N	B
Resting pattern of breathing						
High rate	N	A	A	A	A	A
High tidal air	N	N	A	B	A	A
High minute volume	N	A	A	A	A	A
Low oxygen extraction	B	A	A	B	A	A
Exercise pattern of breathing						
High rate	N	B	B	B	A	A
Low tidal air	B	N	B	B	N	A
Low oxygen extraction	N	N	N	B	A	A
Arterial blood gases						
At rest	N	A	N	N	A	N
After exercise	N	A	N	N	N	-
After oxygen administration	-	N	-	N	A	-
Breath holding	N	N	N	A	A	N
Voluntary breathing capacity	N	A	A	N	A	N
Postural tests	N	N	N	N	N	N
Cardiac output	N	A	N	N	-	N

[a] Listed in order of severity of exposure; A = definitely abnormal; N = normal; B = borderline abnormal; - = not done.

[b] Indicates period at which all special studies were performed, except for arterial blood oxygen, alveolar air oxygen, and carbon dioxide tensions and cardiac output, which were performed 4-8 months later. Symptoms and physical and roentgenographic findings were unchanged on reexamination of all available patients (except No. 5) at that time.

Source: Adapted from Galdston et al. (1947).

returned to work three weeks after discharge. At that time he did not experience any limitation of physical ability. Six months after the accident, pulmonary function studies revealed a disturbance in pulmonary ventilation, but the respiratory function of the lungs was normal. When last examined about a year after his phosgene exposure, he was in good health and did not exhibit any new physical findings.

Case 4: A 48-year-old male was accidentally exposed to phosgene. He experienced a choking sensation, coughed frequently, expectorated tenacious white phlegm, became nauseated, vomited, and felt dizzy. He was admitted to the hospital the next morning and was diagnosed as having acute pulmonary emphysema, edema at the base of each lung, and edema of the pharynx. His medical history revealed previous exposures to both phosgene and chlorine, as well as an inconstant pain in the left side of his chest. The patient had complained of this pain prior to exposure, but his private physician was not able to find its cause.

The patient was discharged from the hospital 19 days after admission. A roentgenogram of the lungs was normal, and he was able to perform moderately heavy work without respiratory distress or fatigue. However, he was able to perform only light work on the job due to pain over the left chest similar to what he had been experiencing for the past six years. Followup examinations three and six months after the accident revealed hyperventilation and abnormalities in pulmonary ventilation consistent with emphysema.

Case 5: A female, age 43, inhaled a "low concentration" of phosgene for about 10 minutes. She experienced sneezing, watering of the eyes, substernal distress, and nausea and vomiting. She was promptly admitted to the hospital where her lungs were found to be clear. Congestion in the conjunctivae and pharynx cleared within a few days; pulmonary edema did not develop. A teleoroentgenogram was interpreted as exhibiting old obliteration of the right costophrenic sulcus, chronic diffuse emphysema, and a partially calcified nodule in the right upper lobe. She was released from the hospital 16 days postexposure, still complaining of cough, weakness, shortness of breath on moderate exertion, and pain over the heart. She was readmitted to the hospital several times in the subsequent months for the same complaints. Pulmonary function studies performed almost six months after the accident showed normal total lung volume; however, other functional abnormalities not related primarily to the rapid, shallow breathing generally recognized as a chronic effect of acute phosgene exposure were seen.

Case 6: A female, age 49, was admitted to the hospital 1.5 hours after inhaling several breaths of phosgene. She was coughing violently, was nauseated and vomiting, and had a nasal and lacrimal discharge. Roentgenograms of the lungs on admission and on the following day appeared normal. There was no leukocytosis, but there was a moderate degree of normocytic anemia. There was no cyanosis or dyspnea, and her lungs were clear throughout. The patient was discharged from the hospital after five days, complaining of pain in the left side of the chest, slight shortness of breath after moderate exertion, and a nonproductive cough. Her past medical history included several minor exposures to phosgene and a fairly serious exposure to chlorine. The patient returned to work, but was unable to work steadily even at light clerical work because of exertional dyspnea, nausea and vomiting after meals, cough, and precordial pain not necessarily associated with effort. At the time of followup, about five months after the accident, X-rays of the gastrointestinal tract, electrocardiograms, and urinalyses were all normal, and the anemia had improved. Pulmonary function studies showed shallow breathing (a typical chronic effect of acute phosgene intoxication) accompanied by moderately impaired intrapulmonary mixing of gases. Mixing was not impaired when respirations were deepened. Respiratory function of the lungs was normal.

From their experience with these phosgene victims, Galdston et al. (1947) were able to draw several conclusions. The chronic symptoms these patients described were similar to those described by gas victims of World War I. A common problem was rapid, shallow breathing that was not severe enough to lead to anoxemia. Breathing oxygen did not alter the pattern of respiration and did not afford consistent relief of symptoms. The measurable changes in pulmonary function that were consistently observed varied in type and severity, but could not be correlated with the severity of phosgene intoxication or with the chronic symptomatology. The severity of this chronic symptomatology and the disability associated with it were closely related to the patients' psychological reactions. Unfortunately, the authors did not address the smoking habits of these patients, and long-term followup studies were not performed.

4.2.6 Secondary Health Effects of Phosgene Poisoning

Most of the published information on phosgene inhalation indicates that it acts solely on the lungs. However, there have been a few reports dating back to World War I indicating effects on other organs, most notably the heart and brain. The most common phosgene-related health effect associated with the brain appears to be neurasthenia. Others include a condition that might be called psychomotor epilepsy, which leads to "drop attacks"; loss of speech coordination; a peripheral Raynaud-like syndrome; and a condition characterized by paralysis of all four limbs with persistent paralysis of the peroneal nerve (Diller, 1985b). Asthma has also been suggested to result from phosgene exposure (Diller, 1985b). Diller attributes these abnormalities to anoxia resulting from pulmonary edema rather than from the direct action of phosgene.

4.3 FACTORS AFFECTING PHOSGENE POISONING

A number of studies have examined the ability of various physical and chemical agents and treatments to alter the severity of phosgene poisoning.

Based on observations made during World War I that eating a large meal shortly after exposure to phosgene increased the severity of poisoning, Cameron (1942) investigated this possibility using laboratory animals. Twenty rats and 10 guinea pigs (strain and sex not specified) were exposed to phosgene at 200 mg/m^3 (50 ppm) for 5 minutes. Ten rats and five guinea pigs were given unlimited food (actual consumption not determined) and the other animals were not allowed to eat, although water was available for all. Twenty-four hours after exposure, there was no significant difference in mortality between fed and unfed animals, but histological evaluation of the lungs of all animals indicated that in rats, the severity of pulmonary edema was greatest in the fed group. No difference was observed in guinea pigs. It was concluded that there was some merit to the observations made during World War I.

Another experiment on the effect of diet on the severity of phosgene intoxication was performed by Calder (1942). One group of 10 rabbits was fed a dry bran diet for 3 days during which their mean body weights decreased by 12.3 percent (206 g). A second group of ten rabbits was fed a normal diet over the same three-day period. These animals showed no significant weight loss. All animals were then exposed to phosgene at 430 mg/m^3 (108 ppm) for 30 minutes. Eighty percent of the rabbits on the normal diet died, whereas only 30 percent of the animals fed the dry bran diet died. The protective effect of the dry bran diet was ascribed to the dehydration it caused with a concomitant reduction in pulmonary edema fluid.

The effect of exercise on the severity of phosgene intoxication has also been investigated. Freeman et al. (1945b) reviewed the literature on the subject and concluded that there is considerable experimental evidence using mice, rats, rabbits, and dogs which uniformly supports the view that moderate exercise during the first few hours after exposure to phosgene does not adversely affect the survival of exposed animals. However, heavy exercise appeared to have an adverse effect.

Boyd (1969) compared death rates in rabbits, cats, and albino rats allowed to inhale the phosgene through the nose (while in an inhalation chamber) to the animals exposed by introducing the gas directly into the trachea by tracheal cannulation. In studies with 18 rabbits exposed to an unspecified dose of phosgene, the mortality rate in tracheal-cannulated rabbits was 88 percent, versus 25 percent in rabbits inhaling phosgene through the nose. The corresponding mortality rates in 14 cats were 100 and 50 percent, and in 80 rats, 90 and 40 percent, respectively. The combined mortality rate in the three species (91 and 39 percent) showed a highly significant difference. The author suggested that since phosgene is fairly labile, the lower toxicity from breathing through the nose may be due to destruction of the gas in the nasobuccopharynx.

Slade et al. (1985) reported that a reduction of lung nonprotein sulfhydryl groups through administration of buthionine sulfoxamine led to an increased edemagenic effect in the lungs of mice, rats, hamsters, guinea pigs, and rabbits exposed to 0.2 ppm phosgene for 4 hours. The authors suggested that nonprotein sulfhydryl may be important in the normal defense of the lung against the toxic effects of phosgene.

4.4 SUMMARY

Animal studies indicate that the severity of a toxic endpoint (e.g., death) following a single inhalation exposure to phosgene is a function of the concentration and length of exposure; CT = K for concentrations ranging from 1 to 200 ppm. However, this relationship does not hold for exposures to very high or very low concentrations of phosgene or when exposure times are not long enough to negate the effects of an animal holding its breath.

Animal studies also indicate that there are very few differences between species in the pathogenesis following acute exposure to phosgene and that the pathogenesis in man is essentially identical to that seen in experimental animals (Bruner and Coman, 1945). In man, exposure to phosgene at concentrations between 3 and 200 ppm causes an immediate irritation of the eyes and throat, and pain or tightness in the chest. The victim may also complain of shortness of breath on exertion, an irritating cough, and nausea and vomiting. These initial symptoms abate rapidly and are followed by the clinical latent phase, which is relatively free of symptomatology. The latent period ends when the amount of edema fluid in the lungs becomes sufficient to interfere with respiration. At this point the patient experiences a definite shortness of breath, a productive cough, and may become anoxic and cyanotic. Death, although rare, usually occurs as a result of paralysis of the respiratory center due to anoxia.

Recovery from acute phosgene intoxication is usually complete, however, most victims of severe poisonings complain of chronic symptoms such as shortness of breath on exertion or reduced physical fitness for several months to several years after the accident. In patients where phosgene poisoning has led to chronic disability, the effects are more closely related to smoking habits, psychological disorders, or preexisting pulmonary abnormalities than to the severity of exposure. Pathological effects to organs other than the lung are rare and are considered to be caused by anoxia, not by a direct action of phosgene.

4.5 REFERENCES FOR CHAPTER 4

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5. SUBCHRONIC AND CHRONIC PHOSGENE EXPOSURE IN ANIMALS

The effects of phosgene have been studied for the most part following acute exposure. Some animal studies are available, however, on the effects of phosgene following repeated exposure over a period of time ranging from a few days to several months. The studies of chronic, low-level phosgene exposure in humans are reviewed in Chapter 6, epidemiology.

5.1 LUNG TISSUE ANALYSIS FOLLOWING SUBCHRONIC PHOSGENE EXPOSURE

Rossing (1964) carried out one of the relatively few studies on subchronic exposure of animals to phosgene. Fourteen mongrel dogs were periodically exposed to 24 to 40 ppm of phosgene for 30 minutes (CT dosages of 720-1200 ppm-min), but remained in the exposure chamber for an additional 30 minutes while all of the phosgene was evacuated. Based on the size of the chamber (1300 L) and the flow rate (600 L/min), it was calculated that about 11 minutes should be required for the gas concentration in the chamber to reach 99 percent of peak. The total amount of phosgene the animals were actually exposed to was measured by drawing gas from the top of the chamber at 1 L/min for the entire exposure period. This sample was bubbled through 0.1N NaOH and the contents of the bubbler subsequently titrated for chloride. It was reported that the actual CT agreed satisfactorily with the calculated value (720-1200 ppm-min), however, the data were not reported.

The animals were exposed in this way three times a week until a definite rise was seen in their airway resistance, at which time the frequency of exposure was reduced to once or twice a week. Animals dying or sacrificed during the exposure period were autopsied and the lungs examined. Of the 14 dogs, 7 died during the first 3 weeks of exposure and 3 were sacrificed at the end of 3 weeks; of the remaining 4 dogs, 1 died during the 11th week and the other 3 completed 12 weeks of exposure, 2 of these being allowed to survive without further exposure. With the exception of these two, all physiologic studies were performed 48 hours after the last exposure to phosgene. Rossing's findings indicated that in the early acute phase there was a sharp rise in dynamic elastance, associated pathologically with extensive edema and inflammation reaction, and coupled with widespread bronchiolar obliterative changes. He suggested that the early change in elastic behavior was largely accounted for by the reduction in the total amount of lung tissue available for ventilation at this time. After the disappearance of the acute inflammatory reaction, there was a progressive resolving bronchiolitis, demonstrated physiologically by a definite increase in lower airway resistance that persists throughout the period of exposure. Microscopic changes suggestive of early, peribronchiolar emphysema were seen. In the two animals allowed to survive beyond the exposure period, elastance dropped rapidly to normal and remained so during the period of observation, but resistance was still elevated in the animals when sacrificed 6 and 11 weeks following exposure.

In another study, Clay and Rossing (1964) exposed adult mongrel dogs (sex not specified) to doses of phosgene ranging from 24 to 40 ppm for 30 minutes, at a rate of 1 to 3 exposures per week to induce experimental emphysema, and studied the changes produced histopathologically. There were four experimental groups of dogs. In Group 1, 7 dogs were exposed 1 or 2 times and sacrificed within 1 or 2 days after the last exposure. In Group 2, 7 animals were exposed 4 to 10 times and sacrificed at various intervals up to 7 days after the last exposure. The 5 dogs in Group 3 were exposed from 15 to 25 times and sacrificed immediately or up to 2 weeks following the last exposure. The 4 animals in Group 4 were exposed 30 to 40 times and sacrificed immediately or as late as 12 weeks after the last exposure.

The authors found that repeated exposure to phosgene produced histologic changes of pulmonary emphysema in dogs. Severe acute or chronic bronchiolitis was produced in all animals exposed one or more times. Acute bronchiolitis involving primarily the bronchioles was consistently found in those animals sacrificed soon after the last exposure. In the chronic cases, the acute changes gave way to chronic obliterative bronchiolitis, and in the cases with the longest exposure, many bronchioles appeared to have disappeared completely or to have been converted into small, inconspicuous fibrous scars.

Cameron and Foss (1941) exposed a group of animals to phosgene at an average concentration of 4.38 mg/m^3 (1.1 ppm) for 5 hours daily for 5 days.

The exposed group consisted of 20 mice, 10 rats, 10 rabbits, 2 cats, and 2 goats. Twenty-four hours after the start of dosing, 50 percent of the mice were dead (10/20); after 48 hours, another 8 died, resulting in a mortality rate of 90 percent in 48 hours (18/20). All mice showed marked mottling of the lungs with congestion, edema, and what was described as emphysema. Two rabbits died after 48 hours (2/10). On examination, one showed large areas of collapse in the lung with congestion and edema. The other rabbit showed some edema and congestion. The remaining animals survived and were killed at the end of the five days of exposure. Microscopic examination of lung tissue from 37 of the animals showed that 22 (59 percent) had lung changes graded as severe, and 15 (41 percent) had mild lung changes. Severe lesions were found in the cats, rabbits, guinea pigs, and mice. The goats and rats were much less affected. Edema was present in 35 of the 37 animals examined (95 percent), with severe edema in 12 animals, moderate edema in 13, and slight edema in 10. All species showed some degree of edema.

In another study by Cameron et al. (1942), the results of exposing several species of animals to phosgene at an average concentration of 0.2 ppm for 5 hours daily for 5 consecutive days were reported. The experimental group consisted of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, and 2 goats. No deaths occurred during the exposures. Except for some labored breathing noted in the cats and in one goat, the animals showed little evidence of distress. At necropsy, pulmonary lesions were seen in 67 percent of the animals. It was reported that the great majority of such lesions were slight and of little significance. Discounting the more susceptible animals (guinea pigs) and correcting for the normal incidence of disease in laboratory animals, the authors estimated that probably between five and ten percent of the animals showed moderately severe lesions. Pulmonary edema was noted in 41 percent of the animals but was considered to be slight in most cases. In six animals (1 mouse, 1 rat, 3 guinea pigs, and 1 rabbit), it was extensive. Acute bronchitis was noted in 22 percent of the animals, and bronchial regeneration was noted in 20 percent. The results are summarized in Table 5-1.

Concentrations of phosgene as low as 0.125 ppm 4 hr/day, 5 days/week for a total of 17 exposure days produced significantly elevated activity of pulmonary glucose-6-phosphate dehydrogenase and non-protein sulfhydryl (glutathione) concentrations in male Sprague-Dawley rats. Small increases were also seen in lung weight at the end of the exposure. These changes appeared to return to

TABLE 5-1. SEVERITY OF PULMONARY LESIONS IN SEVERAL ANIMAL SPECIES EXPOSED TO PHOSGENE (0.2 ppm, 5 hours/day for 5 consecutive days)

	Mice	Rats	G. pigs	Rabbits	Cats	Goats	Total	%
Total no. of animals	20	10	10	10	2	2	54	
Severe lesions	0	1	1	0	0	0	2	4
Mild lesions	1	1	3	1	0	0	6	11
Very slight lesions	13	3	6	5	1	0	28	52
No lesions	6	5	0	4	1	2	18	33
Incidence of pulmonary edema[a]	7(1)	2(1)	7(3)	5(1)	1	0	22	41
Incidence of severe bronchitis	0	1	5	5	1	0	12	22
Incidence of bronchial regeneration	1	1	5	4	0	0	11	20
Incidence of bronchopneumonia	0	1	1	0	0	0	2	4

[a] Numbers in parentheses indicate the number of animals showing fairly severe edema.

Source: Adapted from Cameron et al. (1942).

normal by two days postexposure. These effects were enhanced at 0.25 ppm exposure levels, however, no consistant increase in hydroxyproline (an indicator of collagen accumulation) was seen in the lungs of these animals (Franch and Hatch, 1986).

5.2 PREGASSING PROTECTIVE EFFECT OF PHOSGENE EXPOSURE

Box and Cullumbine (1947) carried out studies in rats and mice to determine whether an initial nonlethal dose of phosgene would diminish the lethality of subsequent exposures to phosgene. In preliminary experiments, it was established that exposure of rats and mice to CT dosages of 600 and 800 mg/m^3-min (150 and 200 ppm-min), respectively, with a 10-minute exposure time, did not normally produce any deaths, although the animals showed all the symptoms of severe phosgene poisoning. Ninety-six rats (of unidentified sex and strain) were divided into 4 groups of 24 each. Twelve rats in each group were exposed to a dosage of 200 ppm-min phosgene, with the other 12 rats in each group serving as controls. Five days later, each group of 24 was exposed for 10 minutes to concentrations of phosgene in the lethal range. The mortalities at the end of 48 hours are shown in Table 5-2.

Statistical analysis demonstrated that there was a lower mortality in the pregassed than in the control animals (Box and Cullumbine, 1947).

In a study to determine the duration of the pregassing protective effect, 70 mice were divided into 7 groups of 10 each. One group was kept as a control, and the other groups were exposed to a phosgene dose of 150 ppm-min at 1, 2, 3, 5, 7, and 10 days before the second gassing. The 70 mice were then exposed to a dosage of 1460 ppm-min, about 3 times the $L(CT)_{50}$. Results indicated that animals in the group pregassed 1 day before died significantly faster, while those pregassed 3, 5, and 7 days before died significantly slower than the control animals. Further studies demonstrated the following: in order to produce the apparent increase of resistance to phosgene, it is necessary to produce lung damage; repeated exposures do not produce a cumulative effect; and rats that have been exposed to a pregassing dose breathe in phosgene more rapidly but take longer to die. The authors concluded that the resistance of pregassed animals can be explained by their more rapid and shallower breathing (determined visually), caused by lung damage in the first exposure (Box and Cullumbine, 1947).

The protective effect of pregassing was also investigated by Henschler and Laux (1960). Twenty Wistar rats (120-150g) were exposed to phosgene at 1 ppm for 6 hours. Four days later, the rats were exposed to phosgene at 18.2 ppm for 30 minutes. The animals that were pregassed with phosgene showed an increase in mean survival time over control animals that were not pregassed. The authors suggested that the protective effect observed could have been due to an enlargement of the alveolar wall caused by the first low-level exposure.

Similar results were demonstrated by Gildemeister in 1921 (as reported in Laqueur and Magnus, 1921). Gildemeister found that cats surviving a phosgene poisoning could be challenged for a second time with a lethal dose of phosgene and still survive. When serum of a previously exposed animal was injected into cats prior to phosgene exposure, mortality was reduced from 64 to 17 percent. Ong (1972) also showed that guinea pigs or mice exposed to increasing doses of phosgene could resist a lethal dose. The same result was obtained after one

TABLE 5-2. MORTALITY OF PREGASSED RATS AND MICE

Exposure dosage (ppm-min)	575	625	785	1100	Total
Mortality in controls	8/12	7/11	9/12	11/12	35/47
Mortality in pregassed animals	3/12	2/12	3/12	8/12	16/48

Source: Adapted from Box and Cullumbine (1947).

exposure to a sublethal dose. Thus, 28 of 33 (85 percent) pregassed animals survived the lethal dose, whereas all of the 15 nontreated control animals died within 24 hours with typical lung edema. In the pregassed animals, a dose that was normally lethal or an even higher dose was administered several times without lethal effect. The tolerance was established within 24 hours and lasted for 3 or 4 months.

Ong (1972) investigated the role of the immune system in the pregassing protective effect. Minced lung from guinea pigs was exposed to a continuous flow of phosgene for two to three hours, and then an extract was made of the phosgene-exposed lung tissue. An antiserum was then prepared by four to five intravenous injections of the extract into rabbits, followed by bleeding the rabbits nine days after the last injection. Four male guinea pigs were then injected intravenously with 2 or 3 mL of antiserum, and 2 to 24 hours later exposed for 20 minutes to phosgene at 41 to 55 mg/m^3 (10-14 ppm), about 1.5 times greater than the previously determined lethal concentration of 31 mg/m^3 (7.6 ppm). Three of four animals survived, the only symptom being a slight anaphylactic shock in one of the surviving animals.

In a second experiment, antiserum was administered to animals exposed to twice the lethal dose of phosgene immediately after gassing. Three of four experimental animals survived, while all four control animals died. Based on statistical evaluation, it was concluded that the antiserum had a definite effect in reducing the mortality of phosgene gassed animals. Further studies indicated that an anaphylactic shock may be produced when antiserum is injected either before or after phosgene poisoning. A high dose of serum, however, tends to reduce the incidence of anaphylactic shock. In order to test the possibility of active immunization against phosgene poisoning, guinea pigs were injected with extract of guinea pig lung exposed to phosgene, and were then exposed to doses of phosgene almost twice the lethal dose at various intervals after injection. It was found that an immunity, lasting for about 60 days, could be induced (Ong, 1972).

Cordier and Cordier (1953) determined the effect of repeated doses of phosgene on cats. In one study, 15 cats were exposed to 20 to 25 mg/m^3 (5-6.2 ppm) for 10 minutes, on a daily basis, for a total of 2 to 41 exposures. No differences were found in animal weights or in histology of lungs of animals exposed to phosgene for a few or many days, even though the animals exposed for the longer periods received several lethal doses of phosgene. It would appear, therefore, that for cats there is no additive effect of phosgene when administered in low daily doses for short periods of time. The authors concluded that there must be either a process of detoxification or of tissue repair going on between each exposure. A second study in six cats demonstrated that 10 to 15 mg/m^3 (2.5-3.7 ppm) of phosgene administered for 10 minutes daily for periods up to 12 days was the lowest dose that induced lung edema.

5.3 OTHER POSSIBLE EFFECTS OF PHOSGENE EXPOSURE

5.3.1 Teratogenicity and Reproductive Effects

No data were found in the literature on teratogenic or reproductive effects of phosgene in humans or animals.

5.3.2 Mutagenicity and Carcinogenicity

No adequate carcinogenicity studies with phosgene have been published. Limited epidemiology studies do not reveal increased incidences in pulmonary or any other tumors in men occupationally exposed to phosgene. However, these epidemiology studies dealt with workers at a single plant and involved relatively small numbers of subjects (see Chapter 6 for details).

The only data available in the literature were in a review on the potential carcinogenicity of 266 chemical substances associated with industrial inhalation exposures (Schepers, 1971). Twenty guinea pigs and 20 rats were dosed with phosgene by inhalation for 24 and 18 months, respectively. Additional information on the study design, including the administered dose or sex and strain of the animals, was not reported. No animals developed pulmonary neoplasms. An additional group of 20 guinea pigs that were found to have a mycobacterial infection also showed no tumors after inhalation exposure to phosgene for 24 months. Helmes et al. (1982) reviewed the literature for information concerning the carcinogenicity and/or mutagenicity of 671 organic chemicals, including phosgene, that were listed as air pollutants by Dorigan et al. (1976). Tables were constructed listing all pollutants considered to be known carcinogens, suspected carcinogens, cocarcinogens, known mutagens, suspected mutagens, or potential carcinogens or mutagens. Phosgene was not listed in any of these categories. Reichert et al. (1983) attempted to determine the mutagenicity of phosgene in a *Salmonella typhimurium* test system, but found it nonmutagenic under the conditions of the assay because it reacted rapidly in the test medium. They detected unchanged phosgene in the solution only above a gaseous concentration of 10,000 ppm.

Although the possibility indeed exists that phosgene may be involved in the hepatocarcinogenicity of chloroform or carbon tetrachloride as a metabolite of these agents during the long-term administration of phosgene, there is no direct evidence that phosgene ever gets past the lungs in unchanged form when animals are exposed to the agent by inhalation. Since essentially all studies on phosgene have been relatively short term, it remains to be seen whether phosgene may be carcinogenic in chronic studies when administered by a route that will permit it to reach susceptible internal organs in unchanged form. However, because of its relatively high toxicity, special considerations are required in designing and performing carcinogenicity studies, including the use of a large number of animals in the experiments. Because there are no adequate animal data on the carcinogenicity of phosgene, and the existing epidemiology studies (see chapter 6) suffer from a lack of exposure data and small numbers of subjects, the available data are judged to be inadequate to assess the human carcinogenic potential for phosgene. According to the Environmental Protection Agency's guidelines for carcinogen risk assessment, phosgene should be considered a group D chemical.

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6. EPIDEMIOLOGY

Relatively few studies have been performed to determine the health effects of chronic low-level phosgene exposure in humans. Those that have been reported indicate that chronic exposure to phosgene at or near the present TLV, often involving some exposures to higher concentrations, does not result in increases in mortality or incidence of cancer. As with the animal studies, there are no reports regarding possible teratogenic or reproductive effects after acute or chronic phosgene exposure.

6.1 URANIUM-PROCESSING PLANT, OAK RIDGE, TN

Polednak (1980) performed an epidemiological study of workers exposed to phosgene from 1943 to 1945 at a uranium-processing plant in Oak Ridge, TN. Phosgene was produced in the "alpha" chemical departments where uranium trioxide was combined with carbon tetrachloride to produce uranium tetrachloride. Phosgene was released into the work environment due to leaks in the reactor and to failures in the scrubber systems that were used to remove the gas. The management attempted to continuously monitor the phosgene levels in the plant; but aside from accidental releases, the concentrations were too low for detection. However, reports from the medical department indicated that exposures to concentrations above 1 ppm occurred 4 or 5 times per day in the "alpha" chemical department. The author therefore assumed that all workers employed in those departments for at least two days during the period 1943 to 1945 had been exposed to phosgene.

Using the records of the Social Security Administration (SSA), Polednak ascertained the vital status (as of 1974) of 699 white males who had worked in the "alpha" department of the plant, as well as a second group of 106 white males who had been involved in accidents which resulted in acute exposures to phosgene at levels reported to be greater than 50 ppm (based on clinical symptoms). The mortality of 9352 white males who worked at the same plant but were not exposed to phosgene was also investigated. Most of controls were employed in various offices, in cafeterias, or in service departments. Cause of death was coded according to the 8th revision of the International Classification of Diseases by a trained nosologist. Expected numbers of deaths were obtained by multiplying death rates for U.S. white males, specific for age (5-year intervals) and calendar year (5-year annual averages) by person-years of followup, which was from the year of first employment at the plant until death, or the end of 1973. Cause-specific standardized mortality ratios (SMR's) were obtained, and 95 percent confidence limits were calculated. These same three cohorts were followed up by Polednak and Hollis (1985) using SSA records for 1979.

The results of both the major and followup studies for the group of chemical workers exposed to low levels are presented in Table 6-1. The discrepancy between the number of subjects per group for the two time periods is due to problems with the SSA records. Approximately 34 percent of the subjects worked less than 2 months in the department of interest; 52 percent worked between 9 and 51 weeks and only 14 percent worked a year or longer.

The SMR's for all causes and for selected cause categories were similar in the chemical worker and control groups, and few SMR's were greater than 100. The relatively low SMR's for all causes, cancers of the digestive organs, and diseases of the nervous, circulatory, genitourinary, and digestive systems were interpreted as being a result of the rather rigid selection of healthy workers at the plant, the "healthy worker" effect, and lower incidence of these ailments for residents of Tennessee as compared to the general U.S. population. The relatively high SMR's for the "senility, ill-defined causes" category is a result of the practice by the State of Tennessee to group deaths from unknown causes into this category. The deaths in the mental, psychoneurotic category of the 699 chemical workers were due to alcoholism.

For the chemical workers (N=699), the SMR's for lung cancer, 127 (95% confidence limit: 66-222) at the end of 1973 and 122 (95% confidence limit: 72-193), at the end of 1978, were slightly elevated but were not significantly higher ($p > 0.05$) than those of the controls (113 and 118) or of the United States population in general (100). The authors did not present data on the smoking habits of the workers or the controls. Increased incidence of death due to diseases of the respiratory system was not seen in the chemical workers exposed to phosgene. Concern was expressed about the 4 observed deaths due to tuberculosis as compared to the 2.8 expected because of reports in the earlier

TABLE 6-1. MORTALITY FROM SELECTED CAUSES AMONG WHITE MALE CHEMICAL WORKERS EXPOSED TO PHOSGENE FROM 1943 TO 1945 AND A CONTROL GROUP OF WHITE MALES WHO WORKED AT THE SAME URANIUM-PROCESSING PLANT, OAK RIDGE, TN

	CHEMICAL WORKERS[a]					
	Observed/expected no. of deaths		SMR (95% CL)[b]		Control SMR's[c]	
Selected causes of death	1974	1979	1974	1979	1974	1979
All causes	151/175	225/232	86(73-101)	97(85-111)	95	101
All infective and parasitic causes	5/4.1	6/4.4	122(40-284)	136(50-297)	80	90
Tuberculosis	4/2.8	4/2.8			91	104
All cancers	30/32	45/46	94(63-134)	99(72-132)	85	89
Cancers of digestive organs	5/9.4	8/13	53(17-123)	62(27-122)	63	66
Lung cancer	12/9.5	18/15	127(66-222)	122(72-193)	113	118
Diseases of blood, blood-forming organs	0/0.5	0/0.6			56	85
Mental, psychoneurotic	2/0.9	3/1.2			141	131
Diseases of the nervous system	1/1.6	1/2.1			68	86
Diseases of the circulatory system	66/87	101/118	75(59-98)	86(70-104)	84	90
Diseases of the respiratory system	7/9.0	14/13	78(31-161)	107(59-180)	113	119
Pneumonia	3/3.5	4/4.6			105	112
Emphysema	2/2.5	4/3.5			111	115
Asthma	0/0.5	0/0.5			77	86
Diseases of the digestive system	6/9.6	8/12	63(23-135)	66(28-130)	76	80
Diseases of the genitourinary system	1/2.8	1/3.3			69	80
Senility, ill-defined causes	7/1.7	8/2.5	402(161-828)	325(140-640)	323	330
External causes	20/21	23/24	96(59-148)	97(62-146)	118	123
Unknown causes[d]	6/-	14/-				

[a] For 1974, n = 699; for 1979, n = 694.

[b] Standardized mortality ratio (SMR), where the expected number is based on death rates for U.S. white males and (in parentheses) the 95% confidence limit. Where the observed number of deaths is less than five, the SMR was not calculated.

[c] For 1974, n = 9352; for 1979, n = 9280.

[d] Death certificates had not yet been obtained.

Source: Adapted from Polednak and Hollis (1985); Polednak (1980).

literature that phosgene exposure in World War I led to the activation of quiescent tuberculosis. However, these observed deaths were not statistically different from the expected values.

A second "acute-exposed" group of white males who worked during the same period at the uranium processing plant were also studied. The 106 men all reported smelling phosgene, and were treated for phosgene poisoning. Symptoms that were commonly reported were irritation of the eyes, nose, or throat; nausea and vomiting; and pain in the chest, dyspnea, and rales. Pneumonitis was found, based on X-rays, in 25 of the patients. One subject died from pulmonary edema due to phosgene poisoning. As of 1974 and 1979, approximately 30 and 35 years after exposure, respectively, 29 and 41 of these men had died, respectively (Table 6-2).

There were no statistically significant differences in any of the cause of death categories between observed and expected deaths. However, due to the small number of individuals in the study, only large increases in mortality would have been detected. None of the subjects died of lung cancer, and only one man died of tuberculosis, at 74 years of age and 32 years after exposure. Deaths due to respiratory diseases were higher in the acute-exposed group, 7 observed versus 3.5 expected as of 1979. One of these men died of "massive lobar pneumonia" in 1959. A second died of "massive chronic bronchiectasis" in 1955. According to company records, neither of these men was diagnosed as having acute respiratory disease after exposure to phosgene. A third man died in 1970 of "chronic bronchitis and emphysema." This individual used tobacco (in 1945) and, after phosgene exposure, had been diagnosed as having "bronchitis" by an examining physician; the bronchitis was attributed to that exposure. The two additional deaths occurred in 1976, 31 years after exposure. One man died of emphysema. He reported using tobacco in 1945 and had a "negative" preemployment chest X-ray and an X-ray diagnosis of chronic bronchitis after phosgene exposure. The second, who died of "chronic obstructive pulmonary disease," had a calcified Ghon tubercle (i.e., evidence of tuberculosis) at preemployment examination but no evidence of pulmonary disease after phosgene exposure; his smoking habits were not recorded.

Polednak and Hollis (1985) have also begun studying 91 female employees at the same plant who had experienced acute accidental exposures to phosgene between 1943 and 1945. However, the data obtained so far are not sufficient to make any conclusions, so further followup is necessary.

TABLE 6-2. SELECTED CAUSES OF DEATH AMONG 106 WHITE MALE WORKERS AFTER ACUTE EXPOSURE TO PHOSGENE BETWEEN 1943 AND 1945

Selected causes of death	Observed/expected no. of deaths 1974	Observed/expected no. of deaths 1979
All causes	29/27	41/34
Tuberculosis	0/0.4	1/0.4
All cancers	2[a]/5	3[a]/6.8
Lung cancer	0/1.5	0/2.2
Diabetes mellitus	1/0.4	1/0.5
Mental, psychoneurotic disorder	2/0.1	2/0.2
Diseases of the circulatory system	12/13	18/17
Diseases of the respiratory system	3/1.4	5/1.9
Pneumonia	1/0.5	1/0.7
Emphysema	0/0.4	1/0.5
Asthma	0/0.1	0/0.1
Diseases of the digestive system	3/1.5	3/1.8
Diseases of the genitourinary system	0/0.4	0/0.5
External causes of death	5[b]/3.1	7[b]/3.5
Accidents	4[b]/2.2	4[b]/2.4
Suicide	1/0.7	2/0.8
Other causes	1/-	1/-
Unknown causes (death certificates not obtained)	1/-	

[a] Cancer of the bladder and pancreas in 1974, and cancer of the large intestine in 1979.

[b] Includes one death from pulmonary edema as a result of phosgene inhalation.

Source: Adapted from Polednak and Hollis (1985); Polednak (1980).

Whereas the execution of the study designs (original study and update) was adequate, the study characteristics severely limit the chronic disease conclusions that can be drawn from these studies. The studies are negative, but because of limiting factors they provide an inadequate basis to assess the carcinogenic and pulmonary disease potential of phosgene. This is particularly true for lung cancer due to the small sample size of the study, and for pulmonary disease due to weaknesses in using the underlying cause of death as a measure of pulmonary system effects.

6.2 EDGEWOOD ARSENAL, MD

Galdston et al. (1947b) followed the case histories of five male employees of the Edgewood Arsenal, Maryland who had repeated exposures to small amounts of phosgene during the course of 1.5 to 3.5 years. Particular emphasis was placed on pulmonary function and on cardiovascular and psychiatric status. The authors presented no data on the frequency or level of exposure to phosgene. The clinical findings on the pulmonary function and cardiovascular status of these patients are presented in Table 6-3.

Case 1: A phosgene worker, age 32, voluntarily entered the Johns Hopkins Hospital on June 26, 1944, for pulmonary function studies. He had experienced conjunctivitis and laryngitis after two exposures to mustard gas in 1941 and 1943. From March 6 through March 9, 1941, he inhaled small amounts of phosgene, which caused a sense of constriction in the chest, dizziness, mental confusion, blurred vision, and severe headaches. He was also exposed to chlorine on July 15, 1941. Additional exposures to phosgene occurred in January 1944, leading to a sensation of tightness in the chest, slight shortness of breath on exertion, and nervous twitchings in different muscles. Clinical examinations in June 1944 revealed a normal red blood count, level of hemoglobin, total and differential white blood counts, and urinalysis. A roentgenogram of the heart and lungs and an electrocardiogram were also normal. However, pulmonary function studies revealed a decrease in vital capacity, impaired intrapulmonary gas mixing, and other changes consistent with pulmonary emphysema. The patient returned to the phosgene plant and was reexamined six months later. There had been no progression of symptoms and there were no new complaints or physical findings.

Case 2: A machinist, age 50, who had worked in the phosgene plant since May 1941, voluntarily entered the Johns Hopkins Hospital on July 9, 1944, for pulmonary function studies. His past history included numerous minor exposures to phosgene that were usually followed by a sense of constriction in the throat, breathlessness, cough, nausea, and vomiting lasting several minutes or hours. He also reported to be suffering from chronic effects of phosgene exposure such as shortness of breath on moderate exertion (for 3.5 years) and a productive cough with sputum that occasionally tasted of phosgene (for the past year). Physical, hematologic, and urinary analyses showed normal results. However, chest roentgenograms and pulmonary function studies showed the presence of pulmonary emphysema. The patient was examined six months later, and there were no new complaints or progression of the symptoms previously noted; physical and laboratory findings were unchanged.

TABLE 6-3. SUMMARY OF CLINICAL FINDINGS IN FIVE WORKERS AFTER CHRONIC OCCUPATIONAL EXPOSURE TO PHOSGENE

Clinical Parameter	Case Number[a]				
	1	2	3	4	5
Age	32	50	24	31	26
Months worked with phosgene	42	36	30	16	30
Chronic symptoms	A	A	A	A	A
Physical signs					
Acute	N	N	N	N	N
Chronic	N	B	A	N	N
Roentgenogram of chest	N	A	A	N	N
Lung volume					
(Vital capacity	A	N	B	N	N
+ % residual air) =					
Total capacity	A	B	A	B	N
Intrapulmonary mixing of gases	A	A	A	A	A
Pulmonary emptying	N	B	A	A	N
Resting pattern of breathing					
High rate	N	A	A	A	N
High tidal air	N	A	A	B	N
High minute volume	N	A	A	A	N
Low oxygen extraction	N	N	B	A	N
Exercise pattern of breathing					
High rate	N	B	B	B	N
Low tidal air	N	N	B	B	N
Low oxygen extraction	N	N	A	A	N
Arterial blood gases					
At rest	N	A	N	N	-
After exercise	N	N	A	A	-
After oxygen administration	N	-	-	-	-
Breath holding	N	A	-	N	N
Voluntary breathing capacity	N	A	A	N	A
Postural tests	N	-	-	-	-
Cardiac output	N	A	N	N	-

[a] Listed in order studied; A = definitely abnormal; N = normal; B = borderline abnormal; - = not done.

[b] Applies to all special studies except arterial blood oxygen, alveolar air oxygen, and carbon dioxide tension studies performed at rest and after exercise, which were done 4-8 months later. Symptoms and physical and roentgenographic findings were unchanged on reexamination of all available patients (except one) at that time.

Source: Adapted from Galdston et al. (1947b).

Case 3: The patient, age 24, voluntarily entered the Johns Hopkins Hospital on July 16, 1944, for pulmonary function studies. His past history included asthma and several minor exposures to chlorine during the winter of 1941. Since early 1942, he had inhaled phosgene at least six times. Acute symptoms were described as immediate coughing, a choking sensation, sweating, nausea and vomiting, and headache. He was usually fully recovered by the next day. He last inhaled phosgene in June 1944, about one month prior to admission to the hospital. Since 1942, the patient had complained of shortness of breath after moderate exertion. Upon examination, urinalysis, hematology, and physical status were all normal except for thoracic kyphosis and bilateral sonorous rales. Roentgenograms and pulmonary function studies indicated the presence of pulmonary emphysema. At a followup examination six months later, the patient was still working in the phosgene plant. There were no new complaints or physical findings, and the symptoms presented on the first admission were still present.

Case 4: The patient, age 31, worked for the Edgewood Arsenal since 1940. His past history included minor exposures to chlorine in 1942 and an exposure to mustard gas in 1943. He began work in the phosgene plant in the fall of 1943 and had at least three exposures to phosgene that caused shortness of breath on moderate exertion and a sticking pain in the chest. Upon voluntary admission to the hospital in August 1944, physical examination revealed a perforated right eardrum and a few sonorous rales at the base of each lung. Roentgenograms of the lungs exhibited only an old obliteration of the left costophrenic angle. Pulmonary function studies revealed abnormalities consistent with pulmonary emphysema. In January 1945, a followup examination showed no new complaints or physical findings; the symptoms previously noted were still present.

Case 5: The patient, age 26, worked in the phosgene plant from January 1942 to February 1943; in the chlorine plant from February 1943 to November 1943; and again in the phosgene plant from November 1943 through August 1944. He reported having a few minor exposures to phosgene that caused burning and watering of the eyes, cough, tightness in the chest, and headache. Since the fall of 1943, the patient had noticed chronic symptoms such as shortness of breath on exertion, tightness in the chest, and occasional attacks of coughing. Upon voluntary admission to the hospital for pulmonary function tests on August 20, 1944, hematology examinations, urinalysis, and physical examination were performed and all indicated normal conditions. A roentgenogram of the heart and lungs was also normal. Results of the pulmonary function studies were normal except for a reduction in voluntary breathing capacity. The patient entered the Navy shortly after the tests; followup and psychiatric examinations were not performed.

Galdston et al. (1947b) have drawn three major conclusions from these five cases: (1) emphysema of the lungs may develop after chronic exposure to phosgene; (2) the measurable disturbances of the lungs are more striking after chronic exposure to phosgene than after recovery from a serious acute poisoning; and (3) the symptoms of chronic exposure to phosgene have not been disabling, in contrast to the frequently prolonged disability seen after acute exposure (Galdston et al., 1947a). Unfortunately, these patients were not subsequently examined, and therefore, no information is available on the fate of the symptomatology after phosgene exposure had been discontinued.

6.3 NIOSH REPORTED STUDIES

The National Institute of Occupational Safety and Health (1976) described three epidemiologic studies in which workers were exposed to phosgene. Two of the studies were translated from Russian and were poorly described by the original authors. Phosgene concentrations were reported to be approximately 0.125 to 0.5 ppm at the work sites, but no increase in pulmonary effects were described. The third study (a written personal communication from A. F. Myers to NIOSH in 1974) compared the medical records of 326 exposed workers at a phosgene plant with those of 6288 nonexposed workers. Pulmonary function, "lung problems," and deaths attributable to respiratory diseases were tabulated for both groups. The author concluded that there were no chronic lung problems associated with working in this phosgene plant and that the exposed workers showed no increased mortality due to respiratory diseases compared to unexposed individuals (Myers, 1974). Phosgene measurements at this plant were made on 15 personal air samples (20-minute collection period) and showed concentrations ranging from nondetected to 0.02 ppm, with an average of 0.003 ppm. Fixed-position air samples (2-hour or 20-minute collection periods) were also taken at the plant; phosgene concentrations in 51/56 samples ranged from nondetected to 0.13 ppm. The remaining five samples showed "off-scale" phosgene concentrations (greater than 0.14 ppm) reportedly due to leaks.

6.4 POISON GAS FACTORY, OKUNOJIMA ISLAND, JAPAN

Nishimoto et al. (1983) investigated the causes of mortality of 2068 male workers employed in a poison gas factory in Japan. The factory produced several poisonous gasses from 1927 to 1945. Phosgene was a relatively minor product; mustard gas and lewisite were produced in the greatest quantity. The authors did not separate the workers according to the gas that they were exposed to; therefore, no conclusions on the long-term health effects of phosgene exposure can be made from this study.

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